Anesthesia for Congenital Heart Disease
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Preface

The third edition of *Anesthesia for Congenital Heart Disease* is a major update and expansion of the textbook that reflects the ongoing development of the practice of pediatric and congenital cardiac anesthesia, and the burgeoning knowledge base in this exciting field. All chapters have been thoroughly revised and updated with new sections and numerous recent references. Additional chapters have been included in two important areas of critical knowledge and practice, addressing anesthetic and sedative neurotoxicity in the patient with congenital heart disease (Chapter 9) and anesthesia in the patient with pulmonary hypertension (Chapter 28). Both of these chapters are written by true experts in these fields and are worthy of their own separate treatment. Also, for the first time, this edition of the textbook is in color, and numerous new illustrations and figures have been added to present a vibrant representation of cardiovascular anatomy and surgical approaches that are essential to the knowledge base for the congenital cardiac anesthesiologist. In addition, after each major section in every chapter, key learning points are presented to highlight important concepts and enhance knowledge retention. Each chapter is accompanied by five multiple-choice questions covering the most crucial learning points in each chapter, to optimize the learning experience for readers at all levels of training and clinical experience. These questions can be found in the on-line book supplement at http://www.wiley.com/go/andropoulos/congenitalheart.

We are pleased to welcome our Texas Children’s Hospital colleague, Wanda C. Miller-Hance, MD, as Co-Editor of this text. Dr. Miller-Hance is a fully trained pediatric and congenital cardiac anesthesiologist, pediatric cardiologist, and recognized authority in intraoperative echocardiography for congenital heart surgery. Reflecting the international scope of anesthesia for congenital heart disease and the many outstanding practitioners all over the world, a number of new international authors have been added from Germany, the United Kingdom, Australia, France, Japan, and Canada.

Finally, caring for patients with congenital heart disease requires a team of dedicated professionals that include congenital cardiac anesthesiologists, congenital heart surgeons, pediatric and adult congenital cardiologists, cardiac intensivists, cardiac interventionalists and imaging specialists, nurses, perfusionists, respiratory therapists, technicians, child life and social workers, and interpreters, among many others. We greatly appreciate the passion and commitment of the people in these disciplines, without whom we could not do our work. Finally, the patient and family are the focus of the team, and their courage and goodwill in the face of serious and complex illness always amaze and inspire us. It is to our patients and their families that *Anesthesia for Congenital Heart Disease*, third edition, is dedicated, in the hope that the knowledge contained in these pages will contribute to better outcomes for them.

It is the purpose of this, our third edition of *Anesthesia for Congenital Heart Disease*, to contribute to the fund of knowledge in our field and to enhance the care of children with heart disease by individuals from various disciplines worldwide.

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Emad B. Mossad, MD  
Wanda C. Miller-Hance, MD
### List of Abbreviations

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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>α₂M</td>
<td>α₂-macroglobulin</td>
</tr>
<tr>
<td>AA</td>
<td>aortic atresia</td>
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<tr>
<td>ABC</td>
<td>Aristotle Basic Complexity</td>
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<tr>
<td>ABO-C</td>
<td>ABO-compatible</td>
</tr>
<tr>
<td>ABO-I</td>
<td>ABO-incompatible</td>
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<tr>
<td>ACE</td>
<td>angiotensin-converting enzyme</td>
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<td>ACGME</td>
<td>Accreditation Council for Graduate Medical Education</td>
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<tr>
<td>ACHD</td>
<td>adult congenital heart disease</td>
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<tr>
<td>ACT</td>
<td>activated clotting time</td>
</tr>
<tr>
<td>ACTH</td>
<td>adrenocorticotropic hormone</td>
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<tr>
<td>AEG</td>
<td>atrial electrogram</td>
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<tr>
<td>AI</td>
<td>aortic insufficiency</td>
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<tr>
<td>AICD</td>
<td>automatic internal cardiac defibrillator</td>
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<td>AIDS</td>
<td>acquired immunodeficiency syndrome</td>
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<tr>
<td>AKI</td>
<td>acute kidney injury</td>
</tr>
<tr>
<td>Akt</td>
<td>protein kinase B</td>
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<tr>
<td>ALCAPA</td>
<td>anomalous left coronary artery arising from the pulmonary artery</td>
</tr>
<tr>
<td>ALI</td>
<td>acute lung injury</td>
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<tr>
<td>ANF</td>
<td>atrial natriuretic factor</td>
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<td>ANH</td>
<td>Acute normovolemic hemodilution</td>
</tr>
<tr>
<td>APAF-1</td>
<td>apoptotic protease activating factor 1</td>
</tr>
<tr>
<td>APERP</td>
<td>accessory pathway effective refractory period</td>
</tr>
<tr>
<td>APOE</td>
<td>apolipoprotein E</td>
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<tr>
<td>APRV</td>
<td>airway pressure release ventilation</td>
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<tr>
<td>aPTT</td>
<td>activated partial thromboplastin time</td>
</tr>
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<td>APW</td>
<td>aortopulmonary window</td>
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<tr>
<td>AR</td>
<td>adrenergic receptor</td>
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<tr>
<td>ARCAPA</td>
<td>anomalous right coronary artery from the pulmonary artery</td>
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<td>ARDS</td>
<td>acute respiratory distress syndrome</td>
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<tr>
<td>ARF</td>
<td>acute renal failure</td>
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<tr>
<td>ASD</td>
<td>atrial septal defect</td>
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<td>ASE</td>
<td>American Society of Echocardiography</td>
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<td>ASO</td>
<td>arterial switch operation</td>
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<td>AT</td>
<td>atrial tachycardia</td>
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<td>ATIII</td>
<td>antithrombin III</td>
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<td>ATP</td>
<td>adenosine triphosphate</td>
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<tr>
<td>AUC</td>
<td>area under the curve</td>
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<tr>
<td>AV</td>
<td>atrioventricular</td>
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<tr>
<td>AVC</td>
<td>atrioventricular canal</td>
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<tr>
<td>AVNRT</td>
<td>atrioventricular nodal re-entry tachycardia</td>
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<td>AVSD</td>
<td>atrioventricular septal defect</td>
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<tr>
<td>BAV</td>
<td>bicuspid aortic valve</td>
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<td>Bax</td>
<td>B-cell lymphoma-2-associated X protein</td>
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<tr>
<td>BCAS</td>
<td>The Boston Circulatory Arrest Study</td>
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<tr>
<td>BCL-2</td>
<td>B-cell lymphoma-2</td>
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<tr>
<td>BCL-xL</td>
<td>B-cell lymphoma-extra large</td>
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<tr>
<td>BCPC</td>
<td>bi-directional cavopulmonary connection</td>
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<td>BDNF</td>
<td>Brain-derived neurotrophic factor</td>
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<tr>
<td>BNP</td>
<td>brain natriuretic peptide</td>
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<tr>
<td>BOS</td>
<td>bronchiolitis obliterans syndrome</td>
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<tr>
<td>BPA</td>
<td>branch pulmonary artery</td>
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<tr>
<td>BPD</td>
<td>bronchopulmonary dysplasia</td>
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<tr>
<td>BSA</td>
<td>body surface area</td>
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<tr>
<td>BSID</td>
<td>Bayley Scales of Infant Development</td>
</tr>
<tr>
<td>BUN</td>
<td>blood urea nitrogen</td>
</tr>
<tr>
<td>C3PO</td>
<td>Congenital Cardiac Catheterization Project on Outcomes</td>
</tr>
<tr>
<td>CABG</td>
<td>coronary artery bypass grafting</td>
</tr>
<tr>
<td>CALM</td>
<td>congenital atresia of the left main coronary artery</td>
</tr>
<tr>
<td>cAMP</td>
<td>cyclic adenosine monophosphate</td>
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<tr>
<td>CAV</td>
<td>coronary artery vasculopathy</td>
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<td>CAVC</td>
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<td>CAVF</td>
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<tr>
<td>CBF</td>
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<tr>
<td>CBG</td>
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<td>CCA</td>
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<tr>
<td>CCAN</td>
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<td>CCB</td>
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<td>CCTGA</td>
<td>congenitally corrected transposition of the great arteries</td>
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<td>Catheterization for Congenital Heart Disease Adjustment for Risk Method</td>
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<td>CICU</td>
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<td>CIED</td>
<td>cardiovascular implantable electronic device</td>
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<td>CIRCI</td>
<td>critical illness-related corticosteroid insufficiency</td>
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<td>CL</td>
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<td>CMR</td>
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<td>CMRO₂</td>
<td>cerebral metabolic rate for oxygen consumption</td>
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<td>CMV</td>
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<td>CO</td>
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<td>COA</td>
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<td>CPB</td>
<td>cardiopulmonary bypass</td>
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<td>catecholaminergic polymorphic ventricular tachycardia</td>
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<td>cerebral–splanchnic oxygen ratio</td>
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<td>CUf</td>
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<td>CVC</td>
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<td>CVVH</td>
<td>continuous veno-venous hemofiltration</td>
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<td>continuous veno-venous hemofiltration and dialysis</td>
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<td>deoxyadenosine triphosphate</td>
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<tr>
<td>DBD</td>
<td>donation after brain death</td>
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<td>DCD</td>
<td>donation after cardiac death</td>
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<tr>
<td>DCM</td>
<td>dilated cardiomyopathy</td>
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<td>DCRV</td>
<td>double-chambered right ventricle</td>
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<td>DHCA</td>
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<td>D-TGA</td>
<td>dextro-transposition of the great arteries</td>
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<td>electrocardiogram</td>
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<td>electroencephalogram</td>
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<td>Food and Drug Administration</td>
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<td>fraction of inspired oxygen</td>
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<td>glucose transporters</td>
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<td>HIV</td>
<td>human immunodeficiency virus</td>
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<tr>
<td>HLA</td>
<td>human leukocyte antigens</td>
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<td>HLHS</td>
<td>hypoplastic left heart syndrome</td>
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<td>HPAM</td>
<td>hypothalamic–pituitary–adrenal axis</td>
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<tr>
<td>HPAH</td>
<td>heritable pulmonary artery hypertension</td>
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<td>HPV</td>
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<tr>
<td>HR</td>
<td>heart rate</td>
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<td>HTK</td>
<td>histidine-tryptophan-ketoglutarate</td>
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<td>HUS</td>
<td>head ultrasound</td>
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<td>IAA</td>
<td>interrupted aortic arch</td>
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<td>IABP</td>
<td>intra-arterial blood pressure</td>
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<td>IAS</td>
<td>interatrial septum</td>
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<td>ICE</td>
<td>intracardiac echocardiography</td>
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<td>ICH</td>
<td>intracranial hemorrhage</td>
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<tr>
<td>ICU</td>
<td>intensive care unit</td>
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<tr>
<td>IE</td>
<td>infective endocarditis</td>
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<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>IgG</td>
<td>immunoglobulin G</td>
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<tr>
<td>IJV</td>
<td>internal jugular vein</td>
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<tr>
<td>IM</td>
<td>intramuscular</td>
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<td>iNO</td>
<td>inhaled nitric oxide</td>
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<tr>
<td>INR</td>
<td>international normalized ratio</td>
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<tr>
<td>IO</td>
<td>inflow occlusion</td>
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<td>IPAH</td>
<td>idiopathic pulmonary artery hypertension</td>
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<td>International Pediatric and Congenital Cardiac Code</td>
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<td>ISHLT</td>
<td>Scientific Registry of the International Society for Heart and Lung Transplantation</td>
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<tr>
<td>IU</td>
<td>international unit</td>
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<tr>
<td>IV</td>
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<td>IVC</td>
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<td>IVH</td>
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<td>JCAHO</td>
<td>Joint Commission for the Accreditation of Hospital Organizations</td>
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<tr>
<td>JET</td>
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<td>KIM-1</td>
<td>kidney injury molecule-1</td>
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<tr>
<td>LA</td>
<td>left atrium</td>
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<tr>
<td>LAA</td>
<td>left aortic arch</td>
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<tr>
<td>LAA</td>
<td>left atrial appendage</td>
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<tr>
<td>LAP</td>
<td>left atrial pressure</td>
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<tr>
<td>LAS</td>
<td>lung allocation score</td>
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<tr>
<td>LBBB</td>
<td>left bundle branch block</td>
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<tr>
<td>LBW</td>
<td>low birth weight</td>
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<td>LBWN</td>
<td>low-birth-weight neonate</td>
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<tr>
<td>LCOS</td>
<td>low cardiac output syndrome</td>
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<td>LE</td>
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<td>L-FABP</td>
<td>liver fatty acid-binding protein</td>
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<tr>
<td>LiDCO</td>
<td>lithium dilution CO</td>
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<tr>
<td>LMA</td>
<td>laryngeal mask airway</td>
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<tr>
<td>LMWH</td>
<td>low-molecular-weight heparin</td>
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<tr>
<td>LPA</td>
<td>left pulmonary artery</td>
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<tr>
<td>LQTS</td>
<td>long QT syndrome</td>
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<td>persistent left superior vena cava</td>
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<tr>
<td>L-TGA</td>
<td>levo-transposition of the great arteries</td>
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<tr>
<td>LV</td>
<td>left ventricle, left ventricular</td>
</tr>
<tr>
<td>LVEDP</td>
<td>left ventricular end-diastolic pressure</td>
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<tr>
<td>LVEDV</td>
<td>left ventricular end-diastolic volume</td>
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<td>LVNC</td>
<td>left ventricular non-compaction</td>
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<tr>
<td>LVOT</td>
<td>left ventricular outflow tract</td>
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<tr>
<td>MAC</td>
<td>minimum alveolar concentration</td>
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<tr>
<td>MAP</td>
<td>mean arterial pressure</td>
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<td>meconium aspiration syndrome</td>
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<td>MAT</td>
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<tr>
<td>mBTS</td>
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<td>MDI</td>
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<td>method of discs</td>
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<td>main pulmonary artery</td>
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<td>mean pulmonary artery pressure</td>
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<td>mitochondrial permeability transition pore</td>
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<td>magnetic resonance imaging</td>
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<td>methicillin-resistant <em>Staphylococcus aureus</em></td>
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<td>OB</td>
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<td>oxygen excess factor</td>
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<td>oxygen extraction rate</td>
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<td>orthotopic heart transplantation</td>
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<td>Organ Procurement and Transplant Network</td>
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<td>p75 neurotrophic receptor</td>
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<td>PA</td>
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<tr>
<td>PA</td>
<td>pulmonary atresia</td>
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<td>PA/IVS</td>
<td>pulmonary atresia with intact ventricular septum</td>
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<td>pharyngeal arch arteries</td>
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<td>PAC</td>
<td>premature atrial contraction</td>
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<td>PaCO₂</td>
<td>partial pressure of carbon dioxide in arterial blood</td>
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<td>preoperative autologous donation</td>
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<td>PAH</td>
<td>pulmonary artery hypertension</td>
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<td>PAH-CHD</td>
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<td>PAPVC</td>
<td>partial anomalous pulmonary venous connection</td>
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<td>partial anomalous pulmonary venous drainage</td>
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<td>protein C</td>
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<td>pressure gradient</td>
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<td>Abbreviation</td>
<td>Description</td>
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<td>pulmonary hypertension</td>
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<td>poly-(4-methyl-1-pentene)</td>
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<td>POCA</td>
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<td>PRA</td>
<td>panel reactive antibody</td>
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<td>PRA</td>
<td>pediatric modification of the RIFLE score</td>
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<td>PRISM</td>
<td>Pediatric Risk of Mortality</td>
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<td>PS</td>
<td>protein S</td>
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<td>PS/IVS</td>
<td>pulmonary stenosis with intact ventricular septum</td>
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<td>prothrombin time</td>
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<td>pulmonary valve</td>
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<td>pulmonary blood flow</td>
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<td>remote ischemic preconditioning</td>
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<td>ROS</td>
<td>reactive oxygen species</td>
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<td>RPA</td>
<td>right pulmonary artery</td>
</tr>
<tr>
<td>RV</td>
<td>right ventricle, right ventricular</td>
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<tr>
<td>RVDCC</td>
<td>right ventricle-dependent coronary circulation</td>
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<td>RVOT</td>
<td>right ventricular outflow tract</td>
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<td>right ventricular outflow tract obstruction</td>
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<tr>
<td>RVSP</td>
<td>right ventricular systolic pressure</td>
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<td>sinoatrial node</td>
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<td>arterial oxygen saturation</td>
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<tr>
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<td>central venous oxygen saturation</td>
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<td>sarcoplasmic reticulum Ca²⁺-ATPase</td>
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<td>shortening fraction</td>
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<tr>
<td>SGOT</td>
<td>serum glutamic oxaloacetic transaminase</td>
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<td>second heart field</td>
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<td>STAT</td>
<td>Society of Thoracic Surgeons–European Association for Cardio-Thoracic Surgery Congenital Heart Surgery mortality score</td>
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<tr>
<td>subAS</td>
<td>subvalvular aortic stenosis</td>
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<td>SV</td>
<td>stroke volume</td>
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<td>SVAS</td>
<td>congenital supravalvular aortic stenosis</td>
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<td>SVC</td>
<td>superior vena cava</td>
</tr>
<tr>
<td>SvO₂</td>
<td>percentage of oxygen saturation of mixed venous blood</td>
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<tr>
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<tr>
<td>SVRI</td>
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<td>supraventricular tachycardia</td>
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<tr>
<td>TA</td>
<td>tricuspid atresia</td>
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<tr>
<td>TAFI</td>
<td>thrombin-activatable fibrinolysis inhibitor</td>
</tr>
<tr>
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<td>total anomalous pulmonary venous connection</td>
</tr>
<tr>
<td>TAPVR</td>
<td>total anomalous pulmonary venous return</td>
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<tr>
<td>TCAD</td>
<td>transplant coronary artery disease</td>
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<td>TDI</td>
<td>tissue Doppler imaging</td>
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<td>transesophageal echocardiography</td>
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<td>tissue factor</td>
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<td>tissue factor pathway inhibitor</td>
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<tr>
<td>TGA</td>
<td>transposition of the great arteries</td>
</tr>
<tr>
<td>TGC</td>
<td>tight glycemic control</td>
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<tr>
<td>TI</td>
<td>tricuspid valve (TV) insufficiency</td>
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<td>total lung capacity</td>
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<tr>
<td>TNF-alpha</td>
<td>tumor necrosis factor-alpha</td>
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<td>TOF</td>
<td>tetralogy of Fallot</td>
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<tr>
<td>TOR</td>
<td>target of rapamycin protein</td>
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<tr>
<td>tPA</td>
<td>tissue plasminogen activator</td>
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<tr>
<td>TPTD</td>
<td>transpulmonary thermodilution</td>
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<tr>
<td>TR</td>
<td>tricuspid regurgitation</td>
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<td>TRALI</td>
<td>transfusion-related acute lung injury</td>
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<tr>
<td>TTE</td>
<td>transthoracic echocardiography</td>
</tr>
<tr>
<td>Abbr.</td>
<td>Description</td>
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</tr>
<tr>
<td>TV</td>
<td>tricuspid valve</td>
</tr>
<tr>
<td>UFH</td>
<td>unfractionated heparin</td>
</tr>
<tr>
<td>UNOS</td>
<td>United Network for Organ Sharing</td>
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<tr>
<td>URI</td>
<td>upper respiratory tract infection</td>
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<tr>
<td>V/Q</td>
<td>ventilation/perfusion</td>
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<tr>
<td>VA</td>
<td>ventriculoarterial</td>
</tr>
<tr>
<td>VAA</td>
<td>volatile anesthetic agent</td>
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<td>VAC</td>
<td>video-assisted cardioscopy</td>
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<td>VAD</td>
<td>ventricular assist device</td>
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<td>video-assisted thoracoscopic surgery</td>
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<td>VF</td>
<td>ventricular fibrillation</td>
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Anesthesia for Congenital Heart Disease: Companion Website

Additional resources to accompany this book are available at:

www.wiley.com/go/andropoulos/congenitalheart

Included on the site:
- MCQ questions to accompany each chapter
- Full reference lists
CHAPTER 1
History of Anesthesia for Congenital Heart Disease

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Introduction

Over the last 70 years, pediatric cardiac anesthesia has developed as a subspecialty of pediatric anesthesia, or a subspecialty of cardiac anesthesia, depending on one’s perspective. It is impossible to describe the evolution of pediatric cardiac anesthesia without constantly referring to developments in the surgical treatment of congenital heart disease (CHD) because of the great interdependency of the two fields. As pediatric anesthesia developed, surgical treatments of children with CHD began to be invented, starting with the simple surgical ligation of a patent ductus arteriosus (PDA), moving on to sophisticated, staged repair of complex intracardiac lesions in low-birth-weight neonates requiring cardiopulmonary bypass (CPB) and circulatory arrest and then on to the most recent complex biventricular repair. Practically every advance in the surgical treatment of CHD had to be accompanied by changes in anesthetic management to overcome the challenges that impeded successful surgical treatment or mitigated morbidity associated with surgical treatment.

This history will mostly be organized around the theme of how anesthesiologists met these new challenges using the anesthetic armamentarium that was available to them at the time. The second theme running through this story is the gradual change of interest and focus from events in the operating room (OR) to perioperative care in its broadest sense, including perioperative morbidity. The last theme is the progressive expansion in the age range of patients routinely presenting for anesthesia and surgery, from the 9-year-old undergoing the first PDA ligation in 1938 [1] to the first fetus to have an intervention for critical aortic stenosis in utero, as reported in The New York Times in 2002 [2], and, more recently, to the adult with CHD.

This story will be told working through the different time frames – the first years (1938–1954); CPB and early repair (1954–1970); deep hypothermic circulatory arrest (DHCA) and introduction of prostaglandin E1 (PGE1) for PDA (1970–1980); hypoplastic left heart syndrome (HLHS) (1980–1990); refinement and improvement in mortality/morbidity (1990–2000); introduction of extracorporeal membrane oxygenation (ECMO) and increased emphasis on interventional cardiology and imaging modalities (2000–2010); expansion to the fetus and adult with CHD (2011); and on to the present time.

The first years: 1938–1954

This period began with the ligation of the PDA and continued with palliative operations. The first successful operation for CHD occurred in August 1938 when Robert E. Gross ligated the PDA of a 9-year-old girl. The operation and the postoperative course were smooth, but because of the interest in the case, the child was kept in the hospital until the 13th day. In the report of the case, Gross mentions...
that the operation was done under cyclopropane anesthesia, and continues: “The chest was closed, the lung being re-expanded with positive pressure anesthesia just prior to placing the last stitch in the intercostal muscles.”

A nurse using a “tight-fitting” mask gave the anesthetic. There was no intubation and, of course, no postoperative ventilation. The paper does not mention any particular pulmonary complications, so it cannot have been much different from the ordinary postoperative course of the day [1].

In 1952, Dr. Gross published a review of 525 PDA ligations where many, if not all, of the anesthetics were administered by the same nurse anesthetist, under surgical direction [3]. Here he states: “Formerly we employed cyclopropane anesthesia for these cases, but since about half of the fatalities seemed to have been attributable to cardiac arrest or irregularities under this anesthetic, we have now completely abandoned cyclopropane and employ ether and oxygen as a routine.” It is probably correct that cyclopropane under these circumstances with insufficient airway control was more likely to cause cardiac arrhythmias than ether. An intralaryngeal airway was used, which also served “to facilitate suction removal of any secretions from the lower airway” (and, we may add, the stomach). Dr. Gross claims that the use of this airway reduced the incidence of postoperative pulmonary complications. Without having a modern, rigorous review of this series, it is hard to know what particular anesthetic challenges other than these were confronted by the anesthetist, but we may assume that intraoperative desaturation from the collapsed left lung, postoperative complications, and occasional major blood loss from an uncontrolled, ruptured ductus arteriosus were high on the list.

The next operation to be introduced was billed as “corrective” for the child with cyanotic CHD and was the systemic to pulmonary artery (PA) shunt. The procedure was proposed by Helen Taussig as an “artificial ductus arteriosus” and was first performed by Albert Blalock at Johns Hopkins Hospital in 1944. In a very detailed paper, Drs. Blalock and Taussig described the first three patients to undergo the Blalock–Taussig shunt operation. Dr. Harmel anesthetized the first and third patients, using ethere and oxygen in an open drop method for the first patient and cyclopropane through an endotracheal tube for the third patient. The second patient was given cyclopropane through an endotracheal tube by Dr. Lamont. Whether the first patient was intubated is unclear, but it is noted that in all three cases, positive pressure ventilation was used to re-inflate the lung [4]. Interestingly, in this early kinder and gentler time, the surgical and pediatric authors reporting the Blalock–Taussig operation acknowledged by name the pediatricians and house officers who took such good care of the children postoperatively, but still did not acknowledge in their paper the contribution of the anesthesiologists Lamont and Harmel. Although intubation of infants was described by Gillespie as early as 1939, it is difficult to say when precisely intubations became routine [5].

Drs. Harmel and Lamont reported in 1946 on their anesthetic experience of 100 operations for congenital malformations of the heart “in which there is pulmonary artery stenosis or atresia.” They reported 10 anesthetic-related deaths in the series, so it is certain that they encountered formidable anesthetic problems in these surgical procedures [6]. This is the first paper we know of published in the field of pediatric cardiac anesthesia.

In 1952, Damman and Muller reported a successful operation in which the main PA was reduced in size and a band was placed around the artery in a 6-month-old infant with a single ventricle (SV). They state that morphine and atropine were given preoperatively, but no further anesthetic agents are mentioned. At that time infants were assumed to be oblivious to pain, so we can only speculate on what was used beyond oxygen and restraint [7].

Over the next 20 years, many palliative operations for CHD were added and a number of papers appeared describing the procedures and the anesthetic management. In 1948 McQuiston described the anesthetic technique used at the Children’s Memorial Hospital in Chicago [8]. This is an excellent paper for its time, but a number of the author’s conclusions are erroneous, although they were the results of astute clinical observations and the knowledge at the time. The anesthetic technique for shunt operations (mostly Potts’ anastomosis) is discussed in some detail, but is mostly of historical interest today. McQuiston explained that he had no experience of anesthetic management used in other centers, such as the pentothal–N₂O–curare used at Minnesota or the ether technique used at the Mayo Clinic. McQuiston used heavy premedication with morphine, pentobarbital and atropine, and/or scopolamine; this is emphasized because it was important “to render the child sleepy and not anxious.” The effect of sedation with regard to a decrease in cyanosis (resulting in making the child look pinker) is noted by the authors. They also noted that children with severe pulmonic stenosis or atresia do not decrease their cyanosis “because of very little blood flow,” and these children have the highest mortality.

McQuiston pointed out that body temperature control was an important factor in predicting mortality and advocated the use of moderate hypothermia (i.e., “refrigeration” with ice bags), because of a frequently seen syndrome of hyperthermia. McQuiston worked from the assumption that hyperthermia is a disease in itself, but did not explore the idea that the rise in central temperature might be a symptom of low cardiac output with peripheral vasoconstriction. Given what we now know about shunt physiology, it is interesting to speculate that this “disease” was caused by pulmonary hyperperfusion after the opening of what would now be considered as an excessively large shunt, stealing a large portion of systemic blood flow.

In 1950 Harris described the anesthetic technique used at Mount Zion Hospital in San Francisco. He emphasized the use of quite heavy premedication with morphine, atropine, and scopolamine. The “basal anesthetic agent” was Avertin (tribromoethanol). It was given rectally and supplemented with N₂O/O₂ and very low doses of curare.
Intubation was facilitated by cyclopropane. The FiO₂ was changed according to cyanosis; and bucking or attempts at respiration were thought to be due to stimulation of the hilus of the lung. This was treated with “cocainization” of the hilus [9].

In 1952 Dr. Robert M. Smith discussed the circulatory factors involved in the anesthetic management of patients with CHD. He pointed out the necessity of understanding the pathophysiology of the lesion and also “the expected effect of the operation upon this unnatural physiology.” That is, he recognized that the operations are not curative. The anesthetic agents recommended were mostly ether following premedication.

While most of these previous papers had been about tetralogy of Fallot (TOF), Dr. Smith also described the anesthetic challenges of surgery for coarctation of the aorta, that was introduced by Dr. Gross in the U.S. and Dr. Craford in Sweden simultaneously in the year 1945. He emphasized the hypertension following clamping of the aorta and warned against excessive bleeding in children operated on at older ages using ganglionic blocking agents. This bleeding was far beyond what anesthesiologists now see in patients operated on at younger ages, before development of substantial collateral arterial vessels [10].


From 1954 to 1970 the development of what was then called the “heart–lung machine” opened the heart to surgical repair of complex intracardiac congenital heart defects. At the time, the initial high morbidity of early CPB technology seen in adults was even worse in children, particularly smaller children weighing less than 10 kg. Anesthetic challenges multiplied rapidly in association with CPB, coupled with early attempts at complete intracardiac repair. The lung as well as the heart received a large share of the bypass-related injuries, leading to increased postoperative pulmonary complications. Brain injury began to be seen and was occasionally reported, in conjunction with CPB operations, particularly when extreme levels of hypothermia were used in an attempt to mitigate the morbidity seen in various organ systems after CPB.

In Kirklin’s initial groundbreaking report of intracardiac surgery with the aid of a mechanical pump–oxygenator system at the Mayo Clinic, the only reference to anesthetic management was a brief remark that ether and oxygen were given [11]. In Lillehei’s description of direct vision intracardiac surgery in humans using a simple, disposable artificial oxygenator, there was no mention of anesthetic management [12]. What strikes a “modern” cardiac anesthesiologist in these two reports is the high mortality: 50% in Kirklin’s series and 14% in Lillehei’s series. All of these patients were children with CHD ranging in age from 1 month to 11 years. Clearly, such mortality and the associated patient care expense would not be tolerated today.

At that time, pediatric anesthesia was performed with open drop ether administration and later with ether using different non-rebreathing systems. Most anesthetics were given by nurses under the supervision of the surgeon. The first physician anesthetist to be employed by a children’s hospital was Robert M. Smith in Boston in 1946.

The anesthetic agent that came into widespread use after ether was cyclopropane; in most of the early textbooks, it was the recommended drug for pediatric anesthesia. Quite apart from being explosive, cyclopropane was difficult to use. It was obvious that CO₂ absorption was necessary with cyclopropane to avoid hypercarbia and acidosis, which might precipitate ventricular arrhythmias. However, administration with a Waters’ absorber could be technically difficult, especially as tracheal intubation was considered dangerous to the child’s “small, delicate airway.”

In all the early reports, it is noted or implied that the patients were awake (more or less) and extubated at the end of the operation. In the description of the postoperative course, respiratory complications were frequent, in the form of either pulmonary respiratory insufficiency or airway obstruction. This latter problem was probably because “the largest tube which would fit through the larynx” was used. Another reason may have been that the red rubber tube was not tissue-tested. The former problem was probably often related to the morbidity of early bypass technology on the lung.

Arthur S. Keats, working at the Texas Heart Institute and Texas Children’s Hospital with Denton A. Cooley, had much experience with congenital heart surgery and anesthesia from 1955 to 1960, and provided the most extensive description of the anesthetic techniques used in this era [13,14]. He described anesthesia for congenital heart surgery without bypass in 150 patients, the most common operations being PDA ligation, Potts’ operation, atrial septectomy (Blalock–Hanlon operation), and pulmonary valvotomy. Premedication was with oral or rectal pentobarbital, chloral hydrate per rectum, intramuscular meperidine, and intramuscular scopolamine or atropine. Endotracheal intubation was utilized, and ventilation was assisted using an Ayres T-piece, to-and-fro absorption system, or a circle system. Cyclopropane was used for induction, and a venous cutoffdown provided vascular access. Succinylcholine bolus and infusion were used to maintain muscle relaxation. Light ether anesthesia was used for maintenance until the start of chest closure, and then 50% N₂O was used as needed during chest closure. Of note is the fact that the electrocardiogram (ECG), ear oximeter, and intra-arterial blood pressure (IABP) recordings were used for monitoring during this period, as well as arterial blood gases and measurements of electrolytes and hemoglobin. The following year he published his experiences with 200 patients undergoing surgery for CHD with CPB, almost all of whom were children. Ventricular septal defect (VSD), atrial septal defect (ASD), TOF, and aortic stenosis were the most common indications for surgery. The anesthetic techniques were
the same as described earlier, except that d-tubocurare was given to maintain apnea during the bypass. In 1957, in addition to ECG, IABP, and oximeter, Dr. Digby Leigh noted the importance of capnography in cardiac surgery. He described the effect of pulmonary blood flow on end-tidal CO₂ (EtCO₂) and the decrease in EtCO₂ after partial clamping of the PA during the Blalock–Taussig shunt procedure. However, it was not until 1995 that Smolinsky et al. reported the importance of EtCO₂ during PA banding [15–17].

Perfusion rates of 40–50 mL/kg/min were used in infants and children, and lactic acidemia after bypass (average 4 mmol/L) was described. No anesthetic agent was added during the bypass procedure, and “patients tended to awaken during the period of bypass,” but apparently without recall or awareness. Arrhythmias noted ranged from frequent bradycardia with cyclopropane and succinylcholine to junctional or ventricular tachycardia, ventricular fibrillation (VF), heart block, and rapid atrial arrhythmias. Treatments included defibrillation, procainamide, digitalis, phenylephrine, ephedrine, isoproterenol, and atropine. Eleven out of 102 patients with VSD experienced atrioventricular block. Epicardial pacing was attempted in some of these patients but was never successful. Fresh citrated whole blood was used for small children throughout the case, and the transfusion of large amounts of blood was frequently necessary in small infants. The mortality rate was 13% in the first series (36% in the 42 patients less than 1 year old) and 22.5% in the second series (47.5% in the 40 patients less than 1 year old). Causes of death included low cardiac output after ventriculotomy, irreversible VF, coronary air emboli, postoperative atrioventricular block, hemorrhage, pulmonary hypertension, diffuse atelectasis, and aspiration of vomitus. No death was attributed to the anesthetic alone. Reading these reports provides an appreciation of the daunting task of giving anesthesia during these pioneering times.

Tracheostomy after cardiac operations was not unusual and in some centers was done “prophylactically” a week before the scheduled operation. These practices were certainly related to primitive (relative to the present) techniques and equipment used for both endotracheal intubation and CPB. Postoperative ventilatory support did not become routine until later when neonatologists and other intensive care specialists had proved it could be done successfully. Successful management of prolonged respiratory support was first demonstrated in the great poliomyelitis epidemics in Europe and the USA in 1952–1954 [18].

Halothane was introduced in clinical practice in the mid-1950s and it rapidly became the most popular agent in pediatric anesthesia, mostly because of the smooth induction compared with the older agents. Halothane was also widely used for pediatric cardiac anesthesia in spite of its depressive effect on the myocardium and the significant risk of arrhythmias. Halothane is no longer available, and the newer inhalational agents, isoflurane and sevoflurane, are now the mainstays of pediatric cardiac cases in US academic centers.

During this period, adult cardiac anesthesiologists, following the practice reported by Edward Lowenstein in 1970 [19], began to use intravenous anesthesia based on opiates. Initially, morphine in doses up to 1 mg/kg was given with 100% oxygen and this technique became the anesthetic of choice for adult cardiac patients, but vasodilation and hypotension associated with its use slowed the incorporation of this technique into pediatric cardiac anesthesia until the synthetic opiates became available.

Before CPB was developed, or when it still carried high morbidity and mortality, a number of modalities were used to improve the outcome for infants. One was inflow occlusion (IO) and another was the hyperbaric chamber. IO was useful and, if well managed, an elegant technique. The secret was the organization of the efforts of the entire operative team, and the technique required the closest cooperation between surgeons and anesthesiologists. The technique was as follows.

The chest was opened in the midline. After pericardiotomy, a side clamp was placed on the right atrial (RA) free wall and an incision made in the RA, or proximal on the PA, prior to placing the vascular clamps used to occlude caval return. Before application of the clamps, patients were hyperventilated with 100% O₂. During IO, the superior vena cava (SVC) and inferior vena cava (IVC) inflow were occluded, ventilation held, and the RA or PA clamp released; the heart was allowed to empty and the septum primum was excised or the pulmonic valve dilated. After excision of the septum or valvotomy, one caval clamp was released initially to de-air the atrium. The RA side clamp or the PA clamp was then reapplied and the other caval clamp released. The heart was resuscitated with bolus calcium gluconate (range 30–150 mg/kg) and bicarbonate (range 0.3–3 mEq/kg). Occasionally, inotropes were administered, most often dopamine. It was important to titrate the inotropes so as not to aggravate rebound hypertension caused by endogenous catecholamines. The duration of the IO was between 1 and 3 minutes – terrifying minutes for the anesthesiologist, but quickly over.

Another modality used to improve the survival after shunt operations, PA banding, and atrial septectomy was to operate in the hyperbaric chamber, thereby benefiting from the increased amount of physically dissolved oxygen. It was a cumbersome affair operating in crowded and closed quarters. There was room for only two surgeons, two nurses, one anesthesiologist, and one baby, as the number of emergency oxygen units limited access. Retired navy divers ran the chamber and kept track of how many minutes the personnel had been in the hyperbaric chamber in the previous week. Help was not readily available because the chamber was buried in a sub-basement and people had to be sluiced in through a side arm that could be pressurized. The chamber was pressurized to 2–3 atmospheres so it was unpleasantly hot while increasing the O₂ pressure and cold while decreasing the pressure;
people with glasses were at a disadvantage. It did not seem to add to survival and was abandoned around 1974.

Anesthesia was a challenge in the hyperbaric chamber. The infants were anesthetized with ketamine and nitrous oxide. As the pressure in the chamber increased, the concentrations of N₂O had to be decreased to avoid the hypotension and bradycardia that occurred rapidly.

Also in this era, the first infant cardiac transplant was performed by Kantrowitz in 1967 [20]. The recipient was an 18-day-old, 2.6 kg patient with severe Ebstein’s anomaly, who had undergone a Potts’ shunt on day 3 of life. The donor was an anencephalic newborn. The anesthetic technique is not described, and the infant died of pulmonary dysfunction 7 hours postoperatively.

The era of deep hypothermic circulatory arrest and the introduction of PGE₁: 1970–1980

Sometime around 1970 physiological repair of CHD, or “correction,” had begun to come of age. In the adult world, coronary bypass operations and valve replacement spurred interest in cardiac anesthesia, which centered increasingly on the use of high-dose narcotics and other pharmacological interventions. As synthetic opiates with fewer hypertensive side-effects became available, their use spread into pediatric cardiac anesthesia in the late 1970s and 1980s.

Children were still treated as “small adults” because major physiological differences were not yet well appreciated, particularly as they related to CPB morbidity. CPB was rarely employed during surgery on children weighing less than 9 kg because of the very high mortality and morbidity that had been experienced in the early years. The notion of repairing complex CHD in infancy was getting attention but was hindered by technical limitations of surgical techniques, CPB techniques, and anesthetic challenges in infants. Theoretically, physiological repair early in life provides a more normal development of the cardiovascular and pulmonary systems and might avoid palliation altogether. The advantage of this was that the sequelae after palliation, for instance distorted pulmonary arteries after shunts and PA banding, might be avoided. Pulmonary artery hypertension following Waterston and Potts’ shunts occurred as a result of increased pulmonary blood flow and resulted in pulmonary vascular obstructive disease. This would not develop if the defect were physiologically repaired at an early age. Furthermore, parents could be spared the anxiety of repeated operations and the difficulties of trying to raise a child with a heart that continued to be impaired.

The perceived need for early repair, together with the high mortality of bypass procedures, in infants and small children led to the introduction of DHCA. It was first practiced in Kyoto, Japan, but spread rapidly to Russia, the west coast of the US at Seattle, Washington, and from there to Midwestern and other US pediatric centers. One example of the difficulties this presented to anesthesiologists was the introduction of DHCA in practice at Boston Children’s Hospital. The newly appointed chief of cardiovascular surgery at the Boston Children’s Hospital was Aldo R. Castaneda, MD, PhD, one of the first supporters of early total correction of CHD, who quickly embraced DHCA as a tool to accomplish his goals for repair in infants. In 1972, he immediately introduced DHCA into practice at Boston Children’s Hospital and the rather shocked anesthesia department had to devise an anesthetic technique to meet this challenge, aided only by a couple of surgical papers in Japanese that Dr. Castaneda kindly supplied. Of course, these papers made little reference to anesthesia.

The first description of the techniques of DHCA from Japan in the English literature was by Horiuchi in 1963 [21]. This involved a simple technique with surface cooling and rewarming during resuscitation, using ether as the anesthetic agent, without intubation. In 1972 Mori et al. reported details of a technique for cardiac surgery in neonates and infants using deep hypothermia, again in a surgical publication [22]. Their anesthetic technique was halothane/N₂O combined with muscle relaxant; CO₂ was added to the anesthetic gas during cooling and rewarming (pH-stat) to improve brain blood flow. The infants were surface-cooled with ice bags and rewarmed on CPB.

Surprisingly, given the enormity of the physiological disturbances and challenges presented by DHCA, very few articles describing an anesthetic technique for DHCA were published, perhaps because DHCA and early correction were not widely accepted. A paper from Toronto described an anesthetic regime with atropine premedication occasionally combined with morphine [23]. Halothane and 50% N₂O were used, combined with d-tubocurare or pancuronium. CO₂ was added to “improve tissue oxygenation by maintaining peripheral and cerebral perfusion.” The infants were cooled with surface cooling (plastic bags with melting ice) and rewarmed on CPB. It was noted that six of the 25 infants had VF when cooled to below 30°C.

Given the lack of any scientific data or studies to guide anesthetic management of such cases, a very simple technique with ketamine–O₂–N₂O and curare supplemented by small amounts of morphine (0.1–0.3 mg/kg) was used at Boston Children’s Hospital. This was the way in which infants were anesthetized for palliative cardiac surgical procedures in the hyperbaric chamber at Boston Children’s Hospital. The infants were surface-cooled in a bathtub filled with ice water to a core temperature of approximately 30°C. The bathtub consisted of a green plastic bucket (for dishwashing) bought at a Sears-Roebuck surplus store, keeping things as simple as possible (Figure 1.1). This method was used in hundreds of infants over the next couple of years and only one infant developed VF in the ice water bathtub. This was an infant with TOF who suffered a coronary air embolus either from a peripheral IV or during an attempted placement of a central venous line. In retrospect, it is amazing that so few
papercouldbe ignored, and as a result make any attempt to study the anesthetic techniques used for DHCA. The published surgical articles were largely unknown to cardiac and pediatric anesthesiologists.

It was during this decade that the “team concept” developed, with cardiologists, cardiac surgeons, and anesthesiologists working together in the OR and the intensive care unit (ICU) in the larger centers. These teams were facilitated by the anesthesiologists’ “invasion” of weekly cardiology–cardiac surgeons’ conferences where the scheduled operations for the week were discussed. Dr. Castaneda, chief surgeon at Boston’s Children’s Hospital, was a leader in the creation of the cardiac team concept for pediatric cardiac surgery.

During the first year of using DHCA in Boston, it was noticed that a number of the infants had “funny, jerky” movements of the face and tongue. A few also had transient seizures during the postoperative period, but as they had normal electroencephalograms (EEGs) at 1-year follow-up, it was felt that significant cerebral complications were not a problem. In view of the knowledge developed subsequently, these clues to neurological damage occurring during and after pediatric cardiac surgery involving DHCA were overlooked. In hindsight, it is perhaps more accurate to say these clues were ignored, and as a result a great opportunity to study this problem was delayed for almost two decades. The issue of neurological damage with DHCA was raised repeatedly by surgeons such as John Kirklin, but was not really studied until the group at Boston Children’s Hospital led by Jane Newburger and Richard Jonas systematically followed a cohort of infants who had the arterial switch operation in the late 1980s using DHCA techniques [24]. In the late 1980s and early 1990s, Greeley and co-workers at Duke performed a series of human studies delineating the neurophysiological response to deep hypothermia and circulatory arrest [25]. These studies provided the crucial data in patients from which strategies for cooling and rewarming, length of safe DHCA, blood gas management, and perfusion were devised to maximize cerebral protection.

Those ongoing studies were followed by a number of other studies comparing DHCA with hypothermic low-flow perfusion, with different hematocrit in the perfusate and with different pH strategies during hypothermic CPB, pH-stat versus alpha-stat.

During those years, the ketamine-morphine anesthetic technique had been supplanted by fentanyl-based high-dose narcotic techniques. For the neurological outcome studies, the anesthetic technique was very tightly controlled, using fentanyl doses of 25 μg/kg at induction, incision, onset of bypass and on rewarming, in addition to pancuronium. From the beginning of this period, surgical results as measured by mortality alone were excellent, with steady increases in raw survival statistics. Because anesthetic techniques were evolving over this period of time, it was difficult to definitely ascribe any outcome differences to different anesthetic agents. A 1984 study of 500 consecutive cases of cardiac surgery in infants and children looked at anesthetic mortality and morbidity. Both were very low – so low in fact that they were probably not universally believed [26].

As the new synthetic opioids such as fentanyl and sufentanil were developed, they replaced morphine to provide more hemodynamic stability in opiate-based anesthetic techniques for cardiac patients. In 1981 Gregory and his associates first described the use of “high-dose” fentanyl 30–50 μg/kg combined with pancuronium in 10 infants undergoing PDA ligation. It is noteworthy that transcutaneous oxygen tension was measured as part of this study. This paper was, in fact, the introduction of high-dose narcotics in pediatric cardiac anesthesia [27]. The technique was a great success; one potential reason for this was demonstrated 10 years later in Anand’s paper showing attenuation of stress responses in infants undergoing PDA ligation who were given lesser doses of fentanyl in a randomized, controlled study [28].

During this same period, synthetic opioids were replacing morphine in adult cardiac surgery. This technique slowly and somewhat reluctantly made its way into pediatric anesthesia [29], replacing halothane and morphine, which had previously been the predominant choice of pediatric anesthesiologists dealing with patients with CHD. In the years from 1983 to 1995, a number of papers were published showing the effect of different anesthetic agents on the cardiovascular system in children with CHD. Ketamine, nitrous oxide, fentanyl, and sufentanil were systematically studied. Some misconceptions stemming from studies of adult patients were corrected, such as the notion that N2O combined with ketamine raises PA pressure and pulmonary vascular resistance (PVR) [30]. On the other hand, the role of increased PaCO2 or lower pH in causing higher PVR was also demonstrated and that subsequently became important in another connection [31]. A number of studies done at this time demonstrated in a controlled fashion the earlier clinical observation (Harmel and McQuiston in the late 1940s) [6,32] that in
cyanotic patients the $O_2$ saturation would rise during induction of anesthesia, almost irrespective of the agent used [33]. These events only serve to reinforce the value of acute clinical observation and provide an example of how the interpretation of such observations may well change as new knowledge is discovered.

**PDA and the introduction of PGE$_1$**

In the mid-1970s, several discoveries were made and introduced into clinical practice that turned out to be of great importance to the pediatric cardiac anesthesiologist and the rest of the cardiac team, the most important being the discovery that PGE$_1$, infused intravenously prevented the normal ducal closure [34]. These developments revolved around the role of the PDA in the pathophysiology of both cyanotic and acyanotic CHD. The critical role of PDA closing and opening in allowing early neonatal survival of infants with critical CHD began to be appreciated and clinicians sought methods of either keeping the PDA open or closing it, depending on what type of critical CHD the neonate was born with and the role of patency of the ductus arteriosus in the CHD pathophysiology. In some cases, particularly in very small neonates, the importance of closing the PDA was increasingly appreciated and, in other cases, the critical importance of maintaining the patency of a PDA was appreciated.

As the survival of very small premature infants (“preemies”) began to improve, mostly because of technical improvements with the use of a warmed isolette and improved mechanical ventilation, it became apparent that in many of these infants the PDA would not undergo the normal closure over time. As the understanding of these infants’ physiological problems improved and more infants survived, the role of continued patency of the PDA in neonates needing mechanical ventilation was appreciated. This led to medical therapy directed at promoting ductal closure using aspirin and indomethacin.

When such attempts failed, it was increasingly understood that necrotizing enterocolitis in the preemie was associated with decreased mesenteric blood flow secondary to the “steal” of systemic blood flow into the pulmonary circulation through a PDA. Thus, in cases when the PDA failed to close in premature infants, the need for operative treatment of the PDA in preemies arose as prophylaxis for necrotizing enterocolitis.

Pediatric and cardiac anesthesiologists were now faced with the task of anesthetizing these tiny preemies safely. This involved maintaining body temperature in infants of 1 kg or less with very large surface area/volume ratios. Intraoperative fluid restriction was important and low levels of $FiO_2$ were used to decrease the risk of retinopathy of prematurity. As the decade progressed, these issues emerged and were addressed. In 1980, Neuman [35] described the anesthetic management of 70 such infants using an $O_2/N_2O$ muscle relaxant anesthesia technique with no mortality. Low $FiO_2$ was used to reduce the risk of retrolental fibroplasia and precautions were taken to prevent heat loss. In those days before human immunodeficiency virus (HIV) became a wide concern, 40% of the infants received blood transfusion. Interestingly, the question of whether to operate in the neonatal intensive care unit (NICU) or the OR for closure of the PDA in the preemie was debated at that time and remains unsettled today.

The PDA lesion presents an interesting story. In 1938 it was the first of the CHD lesions to be successfully treated surgically [1]. In the mid-1970s it was closed with medical therapy, first with aspirin and later with indomethacin. It was the first CHD lesion to be treated in the catheterization laboratory using different umbrella devices or coils [36]. Presently, if surgical closure is necessary, it is often done using a minimally invasive, thoracoscopic video-assisted technique [37]. Thoracoscopy has the benefit of using four tiny incisions to insert the instruments, avoiding an open thoracotomy and limiting dissection and trauma to the left lung. At the same time, this latest development of surgical technique required the anesthesiologist once again to change the anesthetic approach to these patients. Unlike adult anesthesiologists, who can use double-lumen endotracheal tubes for thoracoscopic procedures, pediatric anesthesiologists caring for 1–3 kg infants undergoing PDA ligation do not have the luxury of managing the left lung [37]. Another problem posed by thoracoscopic PDA ligation in the infant is the emerging need for neurophysiological monitoring of the recurrent laryngeal nerve’s innervation of the muscles of the larynx to avoid injury, a known complication of PDA surgery [38]. The last issue is tailoring the anesthetic so that the children are awake at the end of the operation, extubated, and spend an hour or so in the post-anesthesia care unit, bypassing the cardiac ICU. In fact, in 2001, a group led by Hammer at Stanford published the first description of true outpatient PDA ligation in two infants aged 17 days and 8 months [39]. These patients were managed with epidural analgesia, extubated in the OR, and discharged home 10 hours postoperatively. This report brings PDA closure full circle from a 13-day hospital stay following an ether mask anesthetic for an open thoracotomy to a day surgery procedure in an infant undergoing an endotracheal anesthetic for a thoracoscopic PDA ligation.

Maintaining patency of the PDA using PGE$_1$ is probably now of considerably greater importance than its closure both numerically and in terms of being life-sustaining in neonates with critical CHD. The introduction of PGE$_1$ suddenly improved the survival rate of a large number of neonates, with CHD having ductal-dependent lesions to improve pulmonary blood flow, or to improve systemic blood flow distal to a critical coarctation of the aorta. The introduction of PGE$_1$ into clinical practice for therapy of neonatal CHD substantially changed the lives of pediatric cardiac surgeons and anesthesiologists, as frequent middle-of-the-night shunt operations with extremely cyanotic infants almost immediately became a thing of the past. These operations were particularly daunting when one realizes that these procedures were most common before the availability of pulse oximetry; the only warning
signs of impending cardiovascular collapse were the very dark color of the blood and preterminal bradycardia. To get an arterial blood gas with a PaO₂ in the low teens was not uncommon and PaO₂ measurements in single digits in arterial blood samples from live neonates during such surgical procedures were recorded. Even more dramatic was the disappearance of the child with critical post-ductal coarctation. These infants were extremely acidotic, with a pH of 7.0 or less at the start of the procedure (if it was possible to obtain an arterial puncture); they looked mottled and almost dead below the nipples. With the advent of PGE₁ therapy, they were resuscitated medically in the ICU and could be operated on the following day in substantially better condition than was previously the case.

But the introduction of PGE₁ had an effect that was not clearly foreseen except possibly by some astute cardiologists. Survival of a number of these neonates presented pediatric cardiologists and cardiac surgeons (and then anesthesiologists) with rare and severe forms of CHD that had hitherto been considered a “rare” pathological diagnosis. Foremost among these were the infants with HLHS and some forms of interrupted aortic arch. As further experience was gained, it became obvious that these forms of disease were not so rare, but infants who had survived with those forms of CHD were very rare.

**The story of HLHS: 1980–1990**

As mentioned in the previous section, the introduction of PGE₁ brought major changes to pediatric cardiac anesthesiology, solving some problems and at the same time bringing new challenges for the cardiac team. New diagnoses of CHD presented for treatment and were recognized; some had been known previously but had until then presented insurmountable obstacles to any effective therapy.

One of these was HLHS. It had been accurately described in 1958 by Noonan and Nadas but only as a pathological diagnosis [40]. The syndrome is a ductus lesion, with 100% mortality within a few days to weeks when the ductus underwent physiological closure. HLHS was therefore of no practical interest from a therapeutic standpoint until ductal patency could be maintained. When it became possible to keep the ductus arteriosus patent with PGE₁, these neonates rapidly became a problem that could not easily be ignored. In the beginning, most of the infants were misdiagnosed as having sepsis and being in septic shock, and few babies reached the tertiary center without a telltale Band-Aid, indicating a lumbar puncture to rule out sepsis.

But even with the ability to diagnose the defect in a live neonate temporarily kept alive with a PGE₁ infusion, the outlook was not much better. There was no operation devised, and in some centers such neonates were kept viable on a PGE₁ infusion for weeks and even months in the (usually) vain attempt to get them to grow large enough for some surgical procedure to be attempted. In subsequent years, several centers tried different approaches with ingenious conduits, attempting to create an outlet from the right ventricle to the aorta and the systemic circulation.

Those were also the years during which President Ronald Reagan’s Baby Doe regulations were in effect. Anyone who thought an infant was being mistreated (i.e., not operated upon) could call a “hotline number” which was posted in all neonatal ICUs to report the physicians’ “mishandling” of the infant. Fortunately, these regulations died a quiet death after a few chaotic years [41].

In the meantime, the search for a palliative operation went on, also spurred by the increasing success of the Fontan operation, which had been introduced in 1970 [42]. This meant that there was now a theoretical endpoint for HLHS as well as for other forms of SV physiology. It was William Norwood at Boston Children’s Hospital who was the first person to devise a viable palliation and also to complete the repair with a Fontan operation the following year [43]. The publication of this landmark paper spurred considerable discussion. Many cardiologists and surgeons took the position that this operative procedure represented experimental and unethical surgery and that these infants “were better off dead.”

The current approach to these infants varies from multistage physiological repair with palliation followed by Fontan operation. Another alternative is neonatal transplantation as proposed by the group at Loma Linda in California [44]. Some cardiologists are still advocates of conservative “comfort care” for neonates with HLHS. With eventual survival of about 70% being achieved in many centers, these infants can no longer be written off as untreatable. Now the question is more about quality of survival, especially intellectual development. It is also recognized that many have both chromosomal and non-chromosomal anomalies that affect the cerebral and gastrointestinal systems [45].

As was the case from the beginnings of pediatric cardiac surgery, this new patient population presented a management dilemma for the anesthesiologists; they posed a new set of problems that required a solution before acceptable operative results could be achieved. It was obvious that patients with HLHS were hemodynamically unstable before CPB because of the large volume load on the heart coupled with coronary artery supply insufficiency. The coronary arteries in HLHS are supplied from the PDA retrograde through a hypoplastic ascending and transverse aorta that terminates as a single “main” coronary artery. A common event at sternotomy and exposure of the heart was VF secondary to mechanical stimulation. This fibrillation was sometimes intractable, necessitating emergent CPB during internal cardiac massage. This was not an auspicious beginning to a major experimental open heart procedure.

It was during these years that there was a transition from morphine–halothane–N₂O to a high-dose narcotic technique with fentanyl or sufentanil combined with 100%
oxygen. This technique seemed to provide some protection against the sudden VF events compared with historical controls [46]. Despite this modest progress in getting patients successfully onto CPB, it soon became painfully clear that not much progress was made in treating this lesion when trying to wean the patients from bypass. The infants were still unstable coming off bypass and severely hypoxic, and it took some time before we discovered a way to deal with the problem.

A chance observation led to a solution. Infants who came off bypass with low PaO$_2$ (around 30 mmHg) after the HLHS repair often did well, while the ones with immediate “excellent gases” (PaO$_2$ ≥ 40–50 mmHg) became progressively unstable in the ICU a couple of hours later, developing severe metabolic acidosis and dying during the first 24 hours. This observation, combined with discussions with the cardiologists about PVR and systemic vascular resistance (SVR), led to attempts to influence these resistances to assure adequate systemic flow. In retrospect, infants with low PaO$_2$ after bypass had smaller aortopulmonary shunts and adequate systemic blood flow, while those with larger shunts and higher initial PaO$_2$ levels after weaning from bypass tended to “steal” systemic blood flow through the shunt. This would occur in the postoperative period, as the PVR remained elevated as a result of CPB before returning to more normal levels. These observations led to the technique of lowering the FiO$_2$ (sometimes as low as 0.21) and allowing hypoventilation to increase PVR in patients who had larger shunts placed to supply adequate systemic blood flow as part of what became known as the Norwood operation [46]. A different technique used at other institutions to deal with this problem was to add CO$_2$ to the anesthetic gas flow, increasing PVR and continuing to use “normal ventilation” in children who had larger shunts placed and excessive pulmonary blood flow [47]. Both techniques represented different approaches to the same problem: finding ways to deal with the need to carefully balance PVR and SVR after bypass in a fragile parallel circulation in the post-bypass period where dynamic changes were taking place in ventricular function.

These observations, and the subsequent modifications in anesthetic and postoperative management, improved the survival for the stage I palliation (Norwood procedure). It should be noted that the pediatric cardiac anesthesiologist was a full, contributing partner in the progressive improvement in outcome of this very complex and challenging lesion. More importantly, the techniques developed and the knowledge gained in this process also simplified the management of other patients with parallel circulation and SV physiology. The obvious example is truncus arteriosus, where the “usual” ST segment depression and frequent VF that occurred intraoperatively can almost always be avoided. Any decrease in PVR during anesthesia in a child with unrepaird truncus arteriosus can lead to pulmonary “steal” of systemic blood flow and decreased diastolic pressure through the common trunk to the aorta and PA, resulting in hypotension and insufficient systemic blood flow expressed initially as coronary insufficiency and ST depression (or elevation).

During the same decade, the surgical treatment of transposition of the great arteries (TGA) underwent several changes. The Mustard operations (as one type of atrial switch procedure) were feared because of the risk of SVC obstruction as a complication of this surgical procedure. At the end of a Mustard procedure, it was not uncommon to see a child with a grotesquely swollen head having to be taken back to the OR for immediate reoperation. Many of those children suffered brain damage, especially when reoperation was delayed. This resulted from low cerebral perfusion pressure during bypass because of venous hypertension in the internal jugular veins and SVC. The extent and prevalence of such damage were never systematically studied. The arterial pressure during bypass and in the immediate post-bypass period in the OR tended to be low and the pressure in the SVC high. An article from Great Ormond Street in London demonstrated arrested hydrocephalus in Mustard patients [48]. The Senning operation (another variant of the atrial switch approach to TGA) was better, but those children could develop pulmonary venous obstruction acutely in the OR, after the procedure or progressively after hospital discharge. When the diagnosis was not promptly made and acted upon, these infants were often quite sick by the time they came to reoperation.

The successful application of the arterial switch procedure described by Jatene then began to revolutionize operations for TGA [49]. It eliminated the risk of obstruction of the pulmonary and systemic venous return seen after the Mustard and Senning procedures. It also diminished the incidence of the subsequent sick sinus syndrome, a complication that might develop in the first 10 years postoperatively as a result of the extensive atrial suture lines and reconstructions required by these “atrial” switch procedures. The introduction of the arterial switch operation again involved anesthesiologists. The initial attempts at arterial switch operations in many institutions resulted in substantial numbers of infants who had severe myocardial ischemia and even frank infarcts. This was due to a variety of problems with the coronary artery transfer and reimplantation into the “switched” aorta that had been moved to the left ventricle outflow tract. Pediatric cardiac anesthesiologists gained extensive experience with intraoperative pressor and inotropic support and nitroglycerine infusions. They were expected by surgeons to provide support to get infants through what later turned out to be iatrogenically caused myocardial ischemia. As surgeons learned to handle coronary artery transfers and reanastomoses well, these problems largely disappeared, along with the need for major pressor and inotropic support and for nitroglycerine infusion inappropriately directed at major mechanical obstructions in the coronary arterial supply. The arterial switch operation has now been refined at most centers to the point where it is largely a “routine” procedure and it presents, for the most part, no unique anesthetic challenges.
It was during the same time period that a randomized strictly controlled study of stress response in infants undergoing cardiac surgery while anesthetized with high-dose sufentanil was performed. It showed that a high-dose narcotic technique would suppress but not abolish stress responses. It also seemed to show a reduction in morbidity and possibly mortality [50]. However, when the study was refined 10 years later using only high-dose narcotic anesthesia in various techniques, no mortality differences were seen between the various high-dose narcotic techniques. It must be pointed out that the patient population was older and the bypass technique had undergone some refinement [51].

Fontan and the catheterization laboratory: 1990–2000

After the anesthetic technique and preoperative management of the stage I palliation for HLHS had been refined and we had been encouraged by the initial successes of stage II, problems arose. The Fontan operation became problematic as it was applied to younger patients with a great variety of SV types of CHD. Many of the patients had seemingly perfect Fontan operations, but in the cardiac ICU they developed low cardiac output and massive pleural and pericardial effusions postoperatively. Many died in the postoperative period despite a variety of different support therapies; their course over the first 24–48 hours was relentlessly downward and could only be reversed by taking them back to the OR, reversing the Fontan operation and reconstructing a systemic to PA shunt. It was hard for the caretakers of these infants to accept such losses of children they had known from birth. They were our little friends and we knew the families too. All kinds of maneuvers were tried to avoid this sequence of events, from early extubation to the use of a G-suit to improve venous return to the heart. In some centers, a large balloon was placed tightly around the child’s lower body and intermittently inflated by a Bird respirator asynchronous with ventilation.

After a couple of years, two innovations changed the outlook. Both were linked to the understanding that a major limitation of the Fontan operation was the need for a normal or near normal PVR to allow survival through the postoperative period when CPB had caused, through release of a variety of inflammatory mediators and cytokines, a marked elevation of PVR in the early postoperative period. When this bypass-related increase in PVR was associated with younger age (<2 years old) at the time a Fontan was attempted, the higher baseline PVR of the infant made the bypass-related PVR worse and resulted in inadequate pulmonary blood flow and (single) ventricular filling in the early postoperative period, leading to a cycle of low cardiac output, pulmonary and systemic edema, further increases in PVR, acidosis, and death.

One solution was to interpose a bidirectional (Glenn) cavopulmonary anastomosis (BDG) 6–12 months before completion of the Fontan operation. This procedure, and the related operation known as a “hemi-Fontan,” directed only half of the systemic venous return through the lungs at a time when the infant’s PVR had not fallen to normal levels and by preserving an alternative pathway for (single) ventricular filling through systemic venous return not routed through the lungs. This enabled the patients to maintain reasonable cardiac output, although they were a bit “blue” during the early postoperative period, when the PVR had been elevated by CPB. However, this made a third operation, the completion of the Fontan, necessary.

The other innovation was the “fenestrated” Fontan where a small fenestration in the atrial baffle allowed systemic venous return to bypass the lungs as a right-to-left shunt, thereby maintaining ventricular filling and systemic cardiac output during the early postoperative period of high PVR. Over time, the fenestration closed as PVR fell and shunting decreased. Alternatively, a device delivered during an interventional cardiac catheterization could close the fenestrations [52].

This whole process of testing the applicability of the Fontan principle and various modifications of the Fontan operation to a wide variety of types of severe cyanotic CHD involved another set of challenges for the pediatric cardiac anesthesiologist and for collaboration between anesthesiology, cardiology, and surgery. The net result of a great deal of work and collaboration among these groups was that the outlook for the HLHS patients, and indeed for all children with SV defects, improved locally and as these improvements spread and were amplified by work done in other centers, the improvement became national and international. In some institutions, the preferred treatment was and is neonatal transplantation. Its limits are the long waiting time for a transplant, the unavoidable mortality during the waiting period and the ongoing morbidity of neonatal heart transplants, a lifetime of immunosuppression therapy, and the accelerated risk of coronary artery disease seen in heart transplants, even in young children.

The collaboration with pediatric cardiologists around postoperative care of HLHS, Fontan patients, and others spread naturally to the cardiac catheterization laboratory. As pediatric cardiologists began to develop interventional procedures, the need for more control and support of vital functions became apparent. Previously, nurses operating under the supervision of the cardiologist performing the catheterizations had sedated the children for the procedures. In many institutions, this involved high volumes of cases sedated by specially trained nurses, while in others with smaller pediatric caseloads the practice of using general anesthesia for children undergoing cardiac catheterizations had been routine.

The interventional cardiologists turned to pediatric cardiac anesthesiologists for help in managing these patients while the cardiologists themselves were dealing with the complex demands of carrying out interventional procedures in infants and children with CHD. As was the case with newly devised pediatric cardiac surgical procedures, the development of interventional procedures...
for CHD in the cardiac catheterization laboratory posed a whole new set of problems and challenges for pediatric cardiac anesthesia. Not the least of these was providing anesthesia and vital function support in the dark and difficult environment of the cardiac catheterization laboratory. The introduction of dilation techniques for pulmonary arteries and veins, and mitral and aortic valves, and, most recently, the dilation of fetal atrial septal valves in utero along with device closure of the PDA, ASD, and VSD all placed progressively greater demands on the anesthesiologists, who became more and more involved in these procedures.

The development of another set of interventional procedures, the use of radiofrequency ablation to deal with arrhythmias in the pediatric patient, illustrates the progressive complexity and difficulty of anesthesia care in these patients. Initially employed only in healthy teenagers with structurally normal hearts but with paroxysmal atrial tachycardia (PAT), anesthesia care was quite straightforward. Now, in contrast, many of these radiofrequency ablation procedures are done in children with complex CHD, repaired or unrepaired, and frequently the children (or adults) may be quite cyanotic or have low cardiac output [49]. At present, in Boston Children’s Hospital, the cardiac catheterization laboratory and the cardiac magnetic resonance imaging (MRI) unit perform close to 1,500 anesthesia cases per year.

But despite all those developments, the defects remain the same. If we look at the relative distribution of cases in 1982, 2008, and 2013, we see the same diagnoses and a similar numerical relationship between the major groups. As Helen Taussig remarked in her paper about the global distribution of cardiac diagnoses, only surgical interventions change the numbers [53] (see Table 1.1).

### Emergence of technology, including imaging (TEE, MRI) and ECMO: 2000–2010

The first decade of the 21st century saw many changes driven by the availability of new technology, including transesophageal echocardiography (TEE) and cardiac MRI; these, too, provide new challenges for the pediatric cardiac anesthesiologist.

The utility of TEE in congenital heart surgery was demonstrated in the late 1980s by studies of several groups in Japan and the USA, including Russell and Cahalan at the University of California, San Francisco. The use of two-dimensional echocardiography as well as three-dimensional echocardiography improved diagnosis both within and outside the OR and provided more challenges and opportunities for the pediatric cardiac anesthesiologist.

The TEE interpretation of complex CHD and judgment of the adequacy of intraoperative repairs are considerably more challenging in CHD than in adult acquired heart disease. Many centers have called upon pediatric echocardiographers to make such judgments, rather than the pediatric cardiac anesthesiologist being responsible for that as well as for managing the patient in the post-bypass period. In addition, use of TEE has expanded to the cardiac catheterization laboratory where it is used in parallel with fluoroscopy for device closure of septal defects, allowing confirmation of the placement and location of the device [54]. It has been useful in guiding the mechanical support devices, especially the ventricular assist devices (VAD), confirming canula placement and the absence of obstruction [55]. The main concerns for the anesthesiologist when using TEE remain airway obstruction, altering left atrial pressure, or even extubating the child in the middle of an operation “under the drapes”.

Similarly, the emerging availability of cardiac MRI for diagnosis and follow-up of CHD patients has compounded the difficulties of providing anesthesia and monitoring in an intense magnetic field with limited patient access, but requiring anesthesia to be delivered to patients with severe, complex CHD under difficult conditions. Such technological advances come at a high price and it is hard to see how innovations like the long and expensive search for a method of treatment of HLHS would be justified today.

That decade saw another technical innovation of great importance to pediatric cardiac anesthesia: ECMO (Figure 1.2). Use of rapid-response ECMO for children

| Table 1.1 Cardiovascular surgery at Boston Children’s Hospital |
|--------------|-----------|-----------|-----------|
|                | 1982      | 2008      | 2013      |
| Total cases    | (N = 538) | (N = 942) | (N = 1,065) |
| Septal defects | 27%       | 20.1%     | 23.5%     |
| VSD repair     | 12%       | 7.5%      | 10.4%     |
| ASD repair     | 9.6%      | 8.6%      | 10.1%     |
| CAVC           | 5.9%      | 4%        | 3%        |
| Cavopulmonary connection | 3%    | 8.5%      | 6.2%      |
| Fontan procedure | 3%    | 5.4%      | 3%        |
| Bidirectional Glenn | 3.1%  | 3.2%      |           |
| Systemic outflow obstruction | 29%  | 27.1%     | 25.8%     |
| Coarctation     | 7.7%      | 5.1%      | 3.4%      |
| Transposition of great arteries | 5.6%  | 3.5%      |           |
| LVOT repair     | 11.7%     | 13.8%     | 13.4%     |
| Norwood procedure | 3%    | 2.5%      | 2.3%      |
| Biventricular repair | 3.1%  |           |           |
| Pulmonary outflow obstruction | 13%  | 18.2%     | 17.2%     |
| Tetralogy of Fallot repair | 7.6%  | 6.8%      | 3.9%      |
| Conduit placement/revision | 2.8%  | 2.3%      | 3.8%      |
| Other RVOT reconstruction | 1.6%  | 9%        | 9.5%      |
| Pacemaker, AICD placement | 5%    | 3.8%      | 4.5%      |
| Patent ductus arteriosus | 8%    | 6.2%      | 7.2%      |
| Miscellaneous   | 15%       | 16.1%     | 15.6%     |

VSD, ventricular septal defect; ASD, atrial septal defect; CAVC, complete atrioventricular canal; LVOT, left ventricular outflow tract; RVOT, right ventricular outflow tract; AICD, automatic internal cardiac defibrillator.
with CHD who suffer cardiopulmonary collapse postoperatively, who cannot be weaned from CPB, or who need to be supported as a bridge to heart transplantation has proved very effective in reducing mortality rates to astonishingly low levels. In the history of the development of pediatric cardiac anesthesia, we have come a long way from the baby in the ice bath being prepared for DHCA to the complex technology necessary for ECMO resuscitation.

This past decade has also seen a pushing of the envelope to devise new surgical and interventional catheterization approaches that cross the boundaries of the traditional care of patients with CHD and these continue to evolve. Two such approaches are transuterine fetal cardiac catheter intervention (see Chapter 15) and hybrid stage I Norwood palliation (see Chapter 25). The hybrid stage I palliation in the catheterization laboratory requires the anesthesiologist to anticipate and treat significant hemodynamic perturbations, blood loss, and arrhythmias during the procedure, while managing neonatal SV physiology without CPB and providing an anesthetic technique that offers the possibility of early tracheal extubation [56,57]. Hybrid procedures are extending in the catheterization laboratory and include VSD closure, HLHS management, and percutaneous valve implantation. They require a multidisciplinary approach and availability of the cardiac interventionists, cardiac surgeon, and anesthesiologist [58].

2011–2015 and the future

With the understanding that certain cardiac lesions are progressive in nature, prenatal intervention is believed to halt the process in utero and improve the postnatal outcome of these patients. Since the initiation of fetal cardiac interventions, the number of these procedures has been increasing and includes valvuloplasty of the aortic and pulmonary valve, balloon atrial septostomy for restrictive or intact interatrial septum in cases of HLHS and TGA, and fetal pacing in complete heart block. More than 120 cases have been done at Boston Children’s Hospital since 2000 (see Chapter 15). Improving delivery of oxygenated blood to the brain in utero may affect neurodevelopmental outcomes of patients with congenital disease – an area of interest and research [59,60]. Pediatric cardiac anesthesiologists have an integral role in designing and carrying out these procedures. Fetal cardiac intervention for aortic valve stenosis or HLHS with intact atrial septum requires the anesthesia team to induce general anesthesia for the pregnant mother, and also analgesia and muscle relaxation for the fetus, with fetal monitoring by ultrasound [61]. The success of the intrauterine procedures allows potential growth of the ventricle with the goal of a biventricular repair during infancy. However, although the reported success of these procedures is promising, the number of cases and series published is small and does not allow us to conclude superiority over neonatal surgeries and discuss long-term outcomes [62,63].

During fetal interventions, anesthesia is most commonly provided to the fetus by intramuscular injection of opioid, muscle relaxant, and atropine. Most studies comparing anesthetics have been done in animal models. Undergoing a prospective clinical trial in a human fetus has multiple limitations, including the limited number and type of procedures, and their associated complications, the maternal condition, and the lack of time to assess the fetal outcomes during the procedure itself [64].

In the past few years, mechanical circulatory support (MCS) has evolved. Although ECMO remains the most widely used MCS among centers, additional ventricular support devices have been used as a bridge to transplant, leading to an increase in the pediatric cardiac transplant waiting lists [65]. The EXCOR® pediatric VAD (Berlin Heart GmbH, The Woodlands, TX, USA) was recently approved by the US Food and Drug Administration (December 2011).

A study database from 2007 to 2011 (the date of approval of the device) compared the 1-year post-transplant survival between patients who underwent heart transplant without VAD support and those who were bridged with EXCOR to transplant. Pediatric patients supported with EXCOR have similar survival rates to Open Procurement and Transplantation Network status 1A patients supported on either inotropes or ventilator [66].

Children with MCS waiting for cardiac transplant may present for multiple surgeries such as line placements, changes of VAD chamber, chest exploration, and laparotomies. Therefore, an understanding of these devices becomes a must and mandates the presence of a pediatric cardiac anesthesiologist in institutions where surgical care is provided to these patients. Challenges include anticoagulation, thromboembolic and cerebrovascular events, and hemodynamic stability [67]. It is important to be familiar with the device and the adjustment of the settings in order to maintain hemodynamic stability. The VAD output is fixed and dependent on volume. Therefore, hypotension is a concern on induction and maintenance of anesthesia, and the most effective therapy is fluid bolus and alpha-receptor agonist. Cave et al.
recommend ketamine as the drug of choice for patients with assist devices [68,69]. A team approach, including surgical, intensivist, anesthesiologist and the mechanical support team, is of the utmost importance for managing these patients and for coordination during the transport to the operating room or the cardiac catheterization laboratory.

As new treatments in CHD are developed by surgeons and cardiologists, and new technology emerges, the pediatric cardiac anesthesiologist faces new challenges. One significant challenge for the current generation of pediatric cardiac anesthesiologists is to help reduce the cost of care. One of the primary ways to reduce perioperative cost is limit ICU and ventilator time. This translates into increased demands and expectations for early extubation, preferably in the OR. Such changes in care have risks associated with them that will require careful assessment considering the advantages achieved with postoperative ventilation and sedation. For example, arrhythmias and cardiac arrest following endotracheal suctioning in the ICU postoperatively almost disappeared when heavy sedation with fentanyl prevented major swings in PA pressure with suctioning [70,71]. Careful selection of patients for early extubation and judicious use of shorter-acting anesthetic agents may allow lengths of stay to be shortened without increasing risks. In some studies, early extubation after relatively simple operations has, in fact, proved to be safe when using new short-acting anesthetic agents such as sevoflurane and remifentanil, particularly when better pain control is also employed. Other advances, such as limiting the total dose of anesthetic agents by developing ways to monitor depth of anesthesia, so as to give sufficient doses to prevent awareness and attenuate stress responses during CPB, are being explored, but remain elusive [72].

In the past, the outcome criterion most emphasized for treatment of CHD was survival. Now that survival rates are very good and getting better for almost all forms of CHD, attention has turned to the quality of that survival. Recent concerns about the effect of anesthetic agents on the developing brain have prompted extensive efforts to study the magnitude of the effect of these agents, the mechanism of the effect, and whether alternative agents or protective strategies are warranted [73]. Neonatal cardiac surgery patients must have surgery at a vulnerable age and also potentially suffer from brain injury from cyanosis, bypass techniques, inflammation, or low cardiac output, and mechanical support devices are a particularly important focus of study. It has been shown that neurodevelopment is impaired in approximately one-third of children who underwent surgery at a neonatal age [74]. As seen on MRI, 23–40% of neonates presenting with a complex cardiac defect show evidence of cerebral injury preoperatively [75–79]. After surgery, 36–73% of patients have evidence of new cerebral lesions on MRI [75–81]. This suggests that much of the injury develops preoperatively. Therefore, cardiac anesthesiologists may play a key role and are involved in research to ameliorate these effects, including brain imaging and long-term neurodevelopmental outcome studies [82–84]. The new American Heart Association/American Academy of Pediatrics guidelines on the evaluation and management of neurodevelopmental outcomes in children with CHD identifies brain biomarkers and EEG measurements that could be useful in managing patients during the perioperative period [85,86].

**CHD – a growing specialty from the fetus to the adult patient**

*Tempora mutantur et nos in illis* – “Time changes and we develop with time.” It has been 71 years since Robert Gross first ligated a PDA and we have seen amazing developments in the treatment of CHD. Concomitantly, anesthesiology has evolved and slowly defined pediatric anesthesiology, and then cardiac anesthesia, and now, in the past two decades, pediatric cardiac anesthesia has developed as a distinct and separate area of subspecialization.

In 2005, the Congenital Cardiac Anesthesia Society (CCAS; www.pedsanesthesia.org/ccas/) in the USA was formed and now has more than 1,100 members. It provides a forum for subspecialized educational meetings, a national database of congenital cardiac anesthesia cases (see Chapter 3), and has initiated an effort to define adequate postgraduate training in pediatric cardiac anesthesia [87] (see Chapter 2). CCAS is a society organized within the larger Society for Pediatric Anesthesia, indicating that this specialty has chosen to align itself more closely with pediatric anesthesiology than with adult cardiac anesthesiology, although there are important common interests and principles in all three of these specialties caring for patients with CHD.

As part of the trend of increasing long-term survival, the patient care group growing most rapidly at most centers is the adult with CHD. The prevalence of adults in the year 2000 was 49% of patients with CHD [88]. This is the somewhat unexpected result as care in childhood improves and more and more of these patients survive to adulthood and even into old age. At many institutions, special programs have been created to treat these patients and the problems they face. These problems include complications, reoperations, and socioeconomic barriers to normal education, employment, and creation of families. The question of pregnancy and anesthetic management of delivery for these patients is also evolving. It is unclear who is most qualified to provide anesthesia for such patients during labor and delivery. But suddenly the pediatric cardiac anesthesiologist may find themselves having to care for adults [89] (see Chapter 16).

Although there has been much progress in pediatric cardiac anesthesia in providing safe anesthetic care and improving the outcome of treatment of CHD in the OR and catheterization laboratory for patients of all ages, much remains to be done. One can say with certainty that the intimate connection between advances in therapy, surgical or medical, and the anesthesia support services
Figure 1.3 Milestones in the anesthetic management of patients with congenital heart disease. BT, Blalock–Taussig; PDA, patent ductus arteriosus; ASD, atrial septal defect; UI, United States; DHCA, deep hypothermic circulatory arrest; ECG, electrocardiogram; ETCO₂, end-tidal carbon dioxide; ECMO, extracorporeal membrane oxygenation; PCO₂, partial pressure of carbon dioxide; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance; NO, inhaled nitric oxide; U/S, ultrasound; MRI, magnetic resonance imaging; EXCOR, extracorporeal ventricular assist device; FDA, Food and Drug Administration.
required to make those therapeutic advances possible will continue to present new challenges to the pediatric cardiac anesthesiologist. (Figure 1.3) The pediatric cardiac anesthesiologists will, in turn, meet those challenges and in the process find ways to make yet more improvements. Thus we progress in our art and science.

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A full reference list for this chapter is available at:
http://www.wiley.com/go/andropoulos/congenitalheart

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CHAPTER 2

Education for Anesthesia in Patients with Congenital Cardiac Disease

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Introduction

Advances in diagnosis in pediatric cardiology, medical management, cardiac surgery, and cardiac anesthesia throughout the world have drastically increased the survival rate of children with congenital heart disease (CHD) to over 90% and, as a result, there are more adults than children living with CHD today. However, although the heart condition is treated at a young age, the defect is usually considered chronic due to the possibility of increased health issues as a result of experiences or restrictions related to the heart disease itself. The need for greater coordination and integration between pediatric and adult services and a long-term healthcare delivery system is obvious for this patient population. Unfortunately, after leaving pediatric cardiology, many patients are lost to follow-up errors. The specific type of program needed to better ensure all of these patients are “found” and better treated is yet to be discovered, but structured education for adolescents (and their parents), explaining the importance of follow-up, is a vital component.

Anesthesiologists, as an integral part of any system caring for patients with CHD, are often called upon to care for patients ranging in age from neonates to adults. Before the advent of the Congenital Cardiac Anesthesia Society (CCAS) in 2005, there were very few resources in terms of providing training and experience in the specific field of pediatric cardiac anesthesia. The board of directors along with other pediatric anesthesiologists addressed the lack of training criteria in congenital cardiac anesthesia both in the United States and internationally and have developed the resources that we have today.

Why teach and learn congenital cardiac anesthesia?

Only very recently has a curriculum for education in the care of patients with CHD been suggested [1]. Establishment of a curriculum had been complicated by the fact that very few anesthesiologists engage in a practice limited solely to the care of pediatric patients undergoing cardiac surgery. By necessity, most pediatric cardiothoracic anesthesiologists devote some portion of their time to the care of general pediatric patients or to the care of adult cardiothoracic surgical patients. Furthermore, while it has been widely regarded since the 1990s that intraoperative transesophageal echocardiography (TEE) is an accepted standard for the adult cardiac anesthetist, at present there is no formal examination or certification process for pediatric TEE and there is a debate about who (cardiologist or anesthesiologist) is best qualified to perform perioperative pediatric TEE.

The current model

Currently, teaching and learning in congenital cardiothoracic anesthesia more closely resemble an apprenticeship.
model than an established training program. This model has not changed over recent years. Most of this training occurs in a few centers across the US. The type of training received and quality of education are not yet standardized in spite of the efforts taken by these centers of excellence. The “apprenticeship model” as currently practiced does not utilize a structured approach that involves advocating teaching behaviors such as modeling, creating a safe learning environment, coaching, knowledge articulation, and exploration.

A recent publication by the Johns Hopkins group looked at pediatric urology training across the US. This specialty has traditionally used the apprenticeship model. They surveyed 44 pediatric urologists who had completed the 2-year Accreditation Council for Graduate Medical Education (ACGME) approved fellowships and concluded that pediatric urologists feel prepared in commonly performed procedures and perioperative care. The surgeons surveyed reported that faculty feedback/supervision, independent reading, and conferences were rated as a very effective method of teaching.

Saperson discusses the value of changing an apprenticeship model of teaching and educating in psychiatry in Canada to a more competency-based education with explicit expectations. Magen et al. discuss the importance of restructuring training in psychiatry in the US in relation to the healthcare environment. They speculate that funding for graduate medical education programs may be determined by quality measures.

Leong et al. recently completed a survey of pediatric pulmonologists to determine how flexible bronchoscopy is taught to trainees. Based on their survey results, they plan to build a formal competency-based curriculum. Pediatric cardiac surgeons have also recognized that the model to teach trainees to successfully cannulate a pediatric patient for extracorporeal membrane oxygenation (ECMO) based on the apprenticeship model is inadequate. Allan et al. have developed a simulation-based curriculum where they used time to cannulation as a primary endpoint to measure competency [7].

Most trainees also learn from their “role models” in the operating room (OR). In role modeling, faculty members demonstrate clinical skills, and model and articulate expert thought processes. Passi et al. question the value of role modeling in medical education and have conducted an extensive review of the literature to assess the effectiveness of this technique.

**Curriculum for learning and teaching congenital cardiac anesthesia**

Curriculum development should employ a logical, systematic approach linked to specific healthcare needs. The Kern model of curriculum development for medical education could be used to develop a curriculum to teach and learn congenital cardiothoracic anesthesia [9]. This is a six-step approach and consists of the following:

1. Problem identification and general needs assessment
2. Targeted needs assessment
3. Goals and objectives
4. Educational strategies
5. Implementation

**Problem identification and general needs assessment**

This comprises identification and characterization of the healthcare problem:

- Whom does it affect?
- What does it affect?
- What is the qualitative and quantitative importance of the effects?

Education in anesthesia for CHD covers a wide range of lesions – uncorrected, corrected, and palliative therapies. The trainee needs to be educated in all aspects of the six core competencies related to these topics. This is often a daunting task for the educator as well as the trainee. Most traditionally trained pediatric anesthesiologists and adult cardiothoracic anesthesiologists do not have the expertise to manage the unique set of problems presented by this diverse patient population. Although a relationship of clinical outcomes to the training and education level of the healthcare provider has yet to be demonstrated, there is still the potential for a structured curriculum to positively impact quality of care and allocation of healthcare resources. van der Leeuw et al. completed a systematic review of the effect of resident training on patient outcome. They concluded that with adequate supervision, contingencies for additional OR time, and evaluation of and attention to the individual competence of residents throughout residency training could positively serve patient outcomes. There is limited evidence available on the effect of residency training on later practice.

The following points should be addressed to obtain adequate needs assessment:

- What proficiencies (cognitive, affective, and psychomotor skills) currently exist among learners?
- Previous training and experiences of fellows and residents in congenital cardiac anesthesia
- Current training and experiences already planned for trainees
- Resources available to learners (patients and clinical experiences, information resources, computers, audiovisual equipment, role models, teachers, mentors)
- Perceived deficiencies and learning needs
- Characteristics of the learners and barriers to learn and teach.

The current state of anesthesiology training in CHD has recently been characterized in a telephone and email survey performed in 2008 of anesthesia residency program directors (n = 131), ACGME-accredited pediatric anesthesia fellowship directors (n = 45), adult cardiothoracic anesthesia fellowship directors (n = 71; 44 ACGME-accredited, 27 non-ACGME-accredited), and
12-month pediatric cardiac anesthesia fellowship training program directors (n = 3). The following responses summarize training in the USA [1]. Hands-on experience with pediatric cardiac anesthesia during basic anesthesia training is described as “nonexistent” or “rare” in 50% of ACGME-accredited residency programs. In the remaining programs, typical exposure is during the CA-2 and CA-3 years, with residents caring for five to 10 patients requiring procedures with cardiopulmonary bypass (CPB). In a few programs, residents care for as many as 20–30 such patients. Pediatric anesthesia fellows in all 45 ACGME-accredited programs have at least a 2-month cardiac experience during the 12-month fellowship. The typical fellowship experience involves 30–50 CPB cases. In two-thirds of the programs this exposure occurs in 1-month blocks, and in the remainder the experience is distributed throughout the year. Approximately one-quarter of the pediatric fellows use elective time to obtain an additional month or two of experience. Presently, only 13 of the 44 ACGME-accredited and one of the 27 non-accredited fellowships in adult cardiothoracic anesthesia have a mandatory exposure to pediatric cardiac anesthesia, with the remaining programs offering an elective experience of varying duration. Typical mandatory exposure is 1–2 months with 20–30 CPB cases. The words “rarely” or “occasionally” were most commonly used by the individuals surveyed to describe the frequency with which adult cardiothoracic anesthesia fellows use available elective time to pursue training in pediatric cardiac anesthesia. Besides the three known 12-month pediatric cardiac anesthesia fellowships (two in the USA, one in the UK), there were several programs in the USA that offer additional training in pediatric cardiac anesthesia for intervals of 3–12 months on an ad hoc basis.

By 2012, a Second Year Advanced Pediatric Anesthesiology Fellowship Network had been formed in the US, through the efforts of the Pediatric Anesthesia Leadership Council and the Pediatric Anesthesia Fellowship Program Directors’ Association. Pediatric cardiac anesthesia advanced fellowships were included, and a 12-month training period was specified. As of that time, 18 programs were offering these fellowships with a total of 22 available positions.

There is no formal education in TEE at this time for a fellow training in pediatric cardiac anesthesia. This is a skill that is mandated of an adult cardiac anesthesiologist. The model as it stands today in most centers in the US calls for the cardiologist to be in the OR providing the expertise necessary to make intraoperative decisions. It is not currently an expectation that the pediatric cardiac anesthesiologist will have this skill. The question arises as to who is best suited to perform the TEE in the OR. The other question that needs to be answered is how perioperative TEE education will be incorporated into the training model. Will the National Board of Echocardiography devise goals and objectives and a formal assessment of competency?

**Targeted needs assessment**

For the needs assessment to be an accurate reflection of what is required, it must involve the current trainees (learners) in pediatric cardiac anesthesia. Attempts should be made to assess the current strengths and weaknesses in knowledge, skills, and performance [13]. The environment in which the education is currently happening needs to be evaluated as well. Is the OR conducive to education of some of the complex physiology or should the initial education happen in a simulated environment where the stress level of all concerned is much lower? It is vital that all the stakeholders (trainees, program directors, cardiologists, intensivists and pediatric cardiac surgeons) are involved in the development at an early stage. Barriers and reinforcing factors that affect learning should be identified early on. Faculty development programs may be necessary to improve the quality of teaching and education in congenital cardiac anesthesia. Needs assessment should also include what resources are currently available to the trainees to facilitate learning in congenital cardiac anesthesia. The case mix in the training programs, multidisciplinary faculty educators, and access to online journals and educational materials, including the availability of audiovisual equipment, are vital to the success of curricular delivery. The value of the hidden and informal curriculum that is currently in place should not be underestimated.

To date, there have been no reports of needs assessment for curriculum development in congenital cardiac anesthesia in the medical literature. Such an initial needs assessment could be accomplished in the form of a Delphi system, in which global expert opinion as to curriculum needs is sought. This would be an economical method of accessing experts in the field and imposes few geographical limitations. Schinasi et al. used a simulation-based model to perform a needs assessment in procedural sedation among pediatric residents. A study by Haji et al. reported needs assessment for simulation training in neuroendoscopy. The nominal group technique (also known as the expert panel) and the consensus development conference could also be utilized; however, these methodologies are more difficult to organize and are time consuming. Focused group discussions at the annual meeting of the Society for Cardiovascular Anesthesiologists or Society for Pediatric Anesthesia will help deepen information obtained. However a skilled facilitator and note taker are essential so everyone is allowed to voice their opinion and accurate information is recorded. Consideration should be given to the use of the Curriculum Management and Information Tool that is made available by the American Association of Medical Colleges to all medical school faculty. The ultimate goal of the developed curriculum would be to reference objectives, competencies and/or learning outcomes in congenital cardiac anesthesia.
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Goals and objectives

Goals and objectives must, by necessity, be specific and measurable. They should measure the knowledge (cognitive), attitude (affective), and competence (psychomotor) of the learners. The goals and objectives can be developed on the basis of the ACGME core competencies suggested for residency programs. The goals and objectives should reflect the relationship of the educational process to the degree of participation of the learners, as well as the faculty response to the developed curriculum. To achieve goals, the program must be structured to ensure optimal patient care while providing trainees with the opportunity to develop skills in clinical care, judgment, teaching, and research. Consideration should be given to the use of learning goal-scoring rubrics. Meyerson et al. performed a needs assessment for an errors-based curriculum on thoracoscopic lobectomy and structured the curriculum based on their observations using a standardized checklist.

The following goals and objectives are valuable in the OR to achieve competency in congenital cardiac anesthesia:

- The subspecialist in congenital cardiac anesthesiology should be proficient in providing anesthesia care for both pediatric and adult patients undergoing congenital cardiac and vascular surgery as well as anesthesia for non-cardiac surgery.
- The subspecialist should demonstrate and conduct a preoperative patient evaluation; and demonstrate the ability to interpret imaging, cardiovascular, and pulmonary diagnostic test data.
- The subspecialist should be able to evaluate and understand the anesthetic management of patients undergoing non-operative diagnostic and interventional cardiac, thoracic, and electrophysiological procedures. Examples include angiography, arrhythmia mapping and ablation, stent placements, and device closures.
- The clinical curriculum should include competency and demonstrate cognitive proficiency in the management of CPB, pharmacological and mechanical hemodynamic support as well as extracorporeal circulation.
- An advanced skill level in perioperative TEE should be developed and demonstrated as measured by acceptable scores on standardized testing. This skill should be applied on a regular basis in clinical situations and there should be a plan to demonstrate ongoing continuing education in advanced TEE.
- The subspecialist should be able to create a plan for post-operative critical care, including ventilatory support, extracorporeal circulatory support, and pharmacologic hemodynamic support, as well as understand the implications of pain management.
- The subspecialist should demonstrate effective communication skills in obtaining informed consent from families, discussing any complications that may have occurred as well as providing consultations as and when necessary.
- The subspecialist should demonstrate skills in preparing materials and presenting at multidisciplinary conferences to allied health professionals.
- The subspecialist must demonstrate professionalism in the work environment as evidenced by the ability to show compassionate care to the patient and their diverse needs, respecting other providers, as well as complying with program, department, and institutional policies and procedures.
- The subspecialist should understand the value of multidisciplinary teams, be able to evaluate errors, and find solutions, thereby enhancing patient safety and improving outcomes for their patients.

The didactic curriculum provided through lectures, conferences, and workshops should supplement clinical experience as necessary for the fellow to acquire the knowledge to care for cardiothoracic patients with CHD and conditions outlined in the guidelines for the minimum clinical experience for each fellow. The didactic components should include the areas in the following list, with an emphasis on how cardiothoracic diseases affect the administration of anesthesia and life support to cardiothoracic patients with CHD.

These represent guidelines for the minimum didactic experience for each fellow:

- Embryological and morphological development of the cardiothoracic structures; nomenclature of CHD
- Pathophysiology, pharmacology, and clinical management of patients with all adult and pediatric CHD, including single ventricle lesions, septal defects, defects of semilunar and atrioventricular valves, left- and right-sided obstructive lesions, transposition of the great vessels, defects of systemic and pulmonary venous return, cardiomyopathies, vascular rings and tracheal lesions
- Pathophysiology, pharmacology, and clinical management of patients requiring heart, lung, and heart–lung transplantation, including immunosuppressant regimes and selection criteria
- Non-invasive cardiovascular evaluation: electrocardiography, echocardiography, cardiovascular computed tomography (CT), and magnetic resonance imaging (MRI)
- Cardiac catheterization procedures and diagnostic interpretation; invasive cardiac catheterization procedures, including balloon dilatations and stent placement; device closure of septal defects, patent ductus arteriosus and baffle leaks, and arrhythmia ablation
- Pre-anesthetic evaluation and preparation of pediatric and adult cardiothoracic patients
- Pharmacokinetics and pharmacodynamics of medications prescribed for medical management of pediatric and adult cardiothoracic patients
- Peri-anesthetic monitoring methods, both non-invasive and invasive, including use of ultrasound guidance: intra-arterial, central venous, mixed venous saturation, cardiac output determination, transesophageal and epicardial echocardiography, neurological monitoring,
including near-infrared cerebral oximetry, transcranial Doppler, and processed electroencephalograms
• Pharmacokinetics and pharmacodynamics of anesthetic medications prescribed for cardiothoracic patients. Pharmacokinetics and pharmacodynamics of medications prescribed for management of hemodynamic instability: inotropes, chronotropes, vasoconstrictors, vasodilators
• Extracorporeal circulation (including CPB, low-flow CPB, deep hypothermic circulatory arrest, antegrade cerebral perfusion, ECMO), myocardial preservation, effects of extracorporeal circulation on pharmacokinetics and pharmacodynamics, cardiothoracic, respiratory, neurological, metabolic, endocrine, hematomal, renal, and thermoregulatory effects of extracorporeal circulation and coagulation/anticoagulation before, during, and after extracorporeal circulation
• Circulatory assist devices: left and right ventricular assist devices and biventricular assist devices
• Pacemaker and automated internal cardiac defibrillator (AICD) insertion and modes of action
• Perioperative ventilator management: intraoperative anesthetic and critical care unit ventilators and techniques
• Pain management of pediatric and adult cardiothoracic surgical patients. Post-anesthetic critical care of pediatric and adult cardiothoracic surgical patients
• Research methodology and statistical analysis
• Quality assurance and improvement
• Ethical and legal issues
• Practice management.

What is the minimum level of anesthesia training required?

• Subspecialty training in congenital cardiac anesthesiology should begin after satisfactory completion of a residency program in anesthesiology accredited by the ACGME or other training judged suitable by the program director. This track would be consistent with other subspecialty training areas in anesthesiology.
• Trainees could enter the training following completion of an ACGME-accredited adult cardiothoracic anesthesia fellowship of 12 months’ duration after anesthesia residency.
• Trainees could enter the training following completion of an ACGME-accredited pediatric anesthesia fellowship of 12 months’ duration after anesthesia residency.
• Subspecialty training in congenital cardiac anesthesiology could be part of an 18-month continuum in conjunction with an ACGME-accredited pediatric anesthesia fellowship or adult cardiothoracic anesthesiology fellowship after successful completion of an anesthesia residency.
• Recent recommendations as part of the Second Year Advanced Pediatric Anesthesiology Fellowship Network specify a minimum of 12 months of congenital cardiac anesthesiology fellowship training following the 12-month ACGME-first-year pediatric anesthesiology fellowship.

What are the ideal duration, case quantity, and scope of training?

The following represent suggested guidelines for the minimum clinical scope and duration of training:
• Nine months of clinical anesthesia activity caring for patients with congenital cardiac problems in the OR, the cardiac catheterization laboratory, and other locations.
• This experience should include a minimum of 100 anesthetic procedures, the majority of which must require CPB. At least 50 of these patients should be infants from birth to 1 year of age, and should include at least 25 neonates (≤1 month of age). The trainee should also care for at least 25 adults (≥18 years of age).
• This experience should also include a minimum of 50 patients undergoing diagnostic procedures (cardiac catheterization, echocardiography, MRI, etc.), as well as therapeutic procedures in the catheterization laboratory (arrhythmia ablation, pacemaker insertion, septal defect closure and valve dilation, etc.).
• This experience should include a structured intraoperative TEE experience consistent with the practice of intraoperative TEE in the participating program.
• Fellows entering the congenital cardiac anesthesia fellowship following completion of an adult cardiothoracic anesthesia fellowship must complete a 3-month rotation caring for children in the general, non-cardiac ORs to enhance their pediatric anesthesia skills.
• Fellows entering the congenital cardiac anesthesia fellowship following completion of a pediatric anesthesia fellowship or as part of the 18-month congenital cardiothoracic anesthesiology program will complete:
  • A 2-month experience managing pediatric cardiothoracic surgical patients in a critical care (ICU) setting. This experience may include the management of non-surgical cardiothoracic patients. The fellow should actively participate in the management of patients on ECMO.
  • One month of elective rotations (none less than 2 weeks in duration) from the following categories:
    • Echocardiography (TEE and/or transthoracic echocardiography)
    • Extracorporeal perfusion technology
    • Research.
• Experience should be obtained in the preoperative evaluation of pediatric and adult cardiothoracic patients.
• The fellow should understand how to use information from diagnostic studies and how to recognize when additional studies and/or consultations are indicated.

Relationship to other anesthesiology programs

The congenital cardiac anesthesiology program should function in direct association with an ACGME-accredited core anesthesiology program, adult cardiothoracic
anesthesia, or a pediatric anesthesiology program. A congenital cardiac anesthesiology program may be conducted in either a general hospital or a children's hospital. There must be within the same institution as a fully accredited core anesthesiology program or an adult cardiothoracic anesthesiology program or pediatric anesthesiology program with which the congenital cardiac anesthesiology program is associated. The division of responsibilities between trainees in the core anesthesiology program and an associated fellowship program(s) in adult cardiothoracic anesthesiology and/or pediatric anesthesiology must be clearly delineated. The presence of congenital cardiac anesthesiology fellows must not compromise the clinical experience and number of cases available to pediatric anesthesiology fellows and/or core anesthesiology residents. There must be close cooperation between the core anesthesiology program, the adult cardiothoracic anesthesiology program and/or the pediatric anesthesiology program, and the congenital cardiac anesthesiology program.

Educational strategies

Educational strategies involve the content of materials to be delivered in setting of the curriculum as well as the instructional methodology to be used to deliver the content. It will be beneficial to have the fellows involved in the planning of the educational activity. Consideration should be given to forming a committee of responsible faculty members to ensure that the best possible content is delivered.

Content of the curriculum

The driving force here is the learning objectives that have been created in the goals and objectives section. The program director should consider development of a syllabus that includes learning objectives for the lectures, locations of the lectures, any readings that may have to be completed prior to arrival at the educational activity as well as additional resources for the educational activity. All of this information could be made available on a departmental intranet so the fellows have access to it at all times of the day.

Educational methodology

To thrive in today's technologically complex and information-laden clinical environment, pediatric cardiac anesthesiology trainees must become self-directed learners who are able to engage in self-reflection and assessment of their learning needs. To facilitate self-directed learning, program directors and trainees should work together to develop individualized educational plans, learning contracts, and milestone timelines. Here is a list of suggested educational strategies that may be used to address the cognitive, affective, and psychomotor objectives of the curriculum:

- Strategies for achieving cognitive objectives
  - Readings
  - Lectures or large group interactive discussions
  - Audiovisual materials

- Small group discussions
- Self-study modules or web-based learning materials
- Online discussion forums
- Podcasts or streaming video
- Fellow-led didactic sessions
- Systematic reading of stored TEE clips, if included in the curriculum
- Strategies for achieving affective objectives
  - Exposure to, and discussion of, challenging clinical and ethical situations
  - Simulated-learning and cross-training experiences with facilitated debriefing to gain experience in leadership, communication, task delegation, and team development skills
  - Facilitation and modeling of openness, introspection, and reflection through establishment of a safe learning environment
  - Observation of role models, and serving as a role model for anesthesiology residents
  - Standardized patients and role plays
- Strategies for achieving psychomotor objectives
  - Regular supervised clinical experiences with feedback
  - Simulations: partial task trainers, full-body manikins, virtual reality simulators
  - Audiovisual reviews of skills
  - Expert-derived checklists of procedural competence.

In the digital age, there are several tools available to deliver content to the learners. However, all the different methods available may not be suitable for the various objectives to be achieved. Use of self-directed readings, lectures, programmed learning, small group discussions, problem-based discussions, and learning projects is helpful to advance cognitive knowledge. Team-based training, problem-based learning and participation in learning projects all help to cultivate problem-solving skills. However, to teach some of the affective objectives, reflective exercises, discussions and observing role models in the OR may be helpful. To teach skills or competency objectives, the trainee may be taught using simulations, using standardized patients, supervised clinical experiences, artificial models and role playing. All these methods of teaching have pros and cons. They have to be adapted for each individual program and only serve as a guide for program directors. The ideal methodology will encourage active learning, provide immediate feedback to the trainee, promote learning from experience, provide a safe learning environment, facilitate learning of higher cognitive objectives, and promote trainee motivation and responsibility. Utilization of low-cost and less resource-heavy methodologies is also more likely to succeed. Consideration should be given to faculty development if new instructional methodologies are to be utilized.

Conferences should be regularly attended by the trainee, including lectures, interactive conferences, hands-on workshops, morbidity and mortality conferences, cardiac catheterization conferences, echocardiography conferences, cardiothoracic surgery case review conferences, journal reviews, and research seminars. While the faculty
members should be the leaders of the majority of the sessions, active participation by the fellow in the planning and production of these conferences is essential. Attendance at multidisciplinary conferences, especially in cardiovascular medicine, pulmonary medicine, cardiothoracic surgery, vascular surgery, and pediatrics relevant to cardiothoracic anesthesiology, should be encouraged. Provision of an opportunity for fellows to participate in research or other scholarly activities is vital to the success of the educational strategies employed. The fellows must be encouraged to complete a minimum of one academic assignment. Projects may include grand rounds presentations, preparation and publication of review articles, book chapters, and manuals for teaching or clinical practice, clinical research investigation, or similar scholarly activities. A faculty supervisor must be in charge of each project.

In the context of practice-based learning and improvement, trainees should be encouraged to participate in audits of their own patient care and be involved in critical appraisal of clinical practices and the literature. Trainees should be encouraged to develop learning portfolios as well as to create a learning plan for themselves. Learner-driven teaching methodologies are likely to be more successful.

Congenital cardiac anesthesia lends itself nicely to education in the various aspects of systems-based practice and teamwork. Trainees should be involved with quality improvement and attend case conferences focused on cost-effectiveness, patient safety and quality of care as part of a multidisciplinary team. In situ team training has been associated with improved patient outcomes in the setting of pediatric emergencies.

Explicit education in professionalism in the cardiothoracic OR should be promoted by educating the trainees using faculty role models, trainee participation in writing professionalism goals and objectives, and trainee participation in ethics rounds in the intensive care unit (ICU) as part of a multidisciplinary team.

Advances in the Internet have created a number of opportunities for educational material to be easily shared. Most of the content material developed could be posted on the Internet with password-protected access. As the number of physicians training to be providers of anesthesia for CHD is small, this option is attractive. Interesting case discussions, sharing of echocardiographic images, and recent articles pertaining to this area could be posted on the Internet as well. The MedEdPORTAL, Health Education Assets Library (HEAL), CCAS website, and Multimedia Educational Resource for Learning and Online Teaching are some currently available resources that could house the curricular material related to congenital cardiac anesthesia. However, given this wealth of potential educational resources, it is important to keep in mind that the learner should be physically and mentally involved in the learning process. Despite this wealth of potential educational resources, however, it is unclear to what degree anesthesia teachers use these resources as part of their teaching or curricula.

The use of simulation in medical education is also gaining popularity. Simulation allows complex clinical tasks to be broken down into their component parts. Simulation-based medical education can contribute considerably to improving medical care by boosting medical professionals’ performance and enhancing patient safety. Many surgical specialties are looking to simulation as a method for teaching and learning as well as evaluation. There is a role for simulation in learning procedural skills, especially in the climate of decreasing clinical exposure. Recent meta-analysis of the use of simulation in anesthesia training showed inconsistency in measurement of non-technical skills and consistency in the (ineffective) design of debriefing [23]. There is also evidence in the surgical literature that virtual reality training can improve OR performance. In a recent meta-analysis, a simulation-based airway management curriculum appeared superior to no intervention and non-simulation intervention for important education outcomes. Consideration should be given to the use of a clinical skills laboratory to pre-teach some of the skills necessary in the management of a complex patient population [25].

Anesthesia for CHD is a high-risk, low-error tolerance field. The fundamental knowledge and skills that congenital cardiac anesthesiologists will need to master if they are to increase their capacity to attain higher levels of performance are considerable. A clinical microsystems model may prove useful to facilitate the development of this fundamental knowledge and skills using the action-learning theory and sound education principles to provide the opportunity to learn, test, and gain some degree of mastery.

**Implementation**

Once a curriculum has been developed, it is the role of the program director to oversee its successful implementation. Success is achieved through insightful leadership, transparency and constant communication, forethought and general administration of the program, continuous quality improvement efforts, and establishment and maintenance of a stable educational environment. The program director must possess the requisite specialty expertise and have training and/or clinical experience in providing anesthesia care for congenital cardiac surgical patients that meets or exceeds that associated with completion of a 1-year congenital cardiac anesthesia fellowship program. To implement a new curriculum, the program director must possess the necessary administrative and educational knowledge and skills to:

- identify necessary materials and resources
- obtain administrative and, if necessary, financial support
- identify and recruit qualified faculty members
- provide faculty development and teacher training
- develop administrative mechanisms to support the curriculum
- identify appropriate teaching space (e.g. in the OR, simulation center, or other appropriate clinical venues)
- anticipate and address barriers.
Above all else, the program director is responsible for keeping faculty, learners, and staff informed about plans for implementing a new curriculum. Individuals who are expected to support, teach, or participate in program must be made aware of the program’s design, educational strategies, and assessment methods in order to ensure its smooth execution. The program director should also present curricular updates, especially any successes or milestones achieved, to identified stakeholders. Stakeholders are people with an interest in the program and its evaluation and may include the pediatric anesthesia department chair, cardiothoracic anesthesia division chief, anesthesia residency program director, other anesthesia subspecialty fellowship directors, funding agencies, and/or hospital administrators (e.g. the Vice President for Quality and Safety).

While the program director is responsible for overseeing the curriculum, this does not have to be done in isolation. There are a number of faculty and staff members who can provide support and advice regarding the design and teaching of a curriculum. As an added benefit, those involved at the front end of a program’s design and implementation are more likely to want to participate in teaching and assessing the curriculum. A junior faculty member with expertise in congenital cardiac anesthesiology and interest in medical education may be eager to help develop and present a curriculum. Pediatric anesthesia faculty members with previous curriculum development experience as well as clinician educators committed to anesthesiology training in CHD may be recruited as educational consultants and then later asked to teach in the program. Involving other faculty members in the development and implementation of a curriculum also ensures a program’s continuity, stability, and sustainability.

There are several key decisions that must be made, and steps that must be taken, before implementing a congenital cardiac anesthesia curriculum. First the program director needs to decide whether to introduce the curriculum as a pilot program, in stages, or to present it in its entirety. There are arguments for and against each approach; however, if stakeholders are wary of a new curriculum’s educational benefit, it is best to introduce a pilot program in order to collect evidence of its value and then gain support for its full implementation. Recruiting faculty members and then developing them to teach in the program are further essential steps. To present a successful and sustainable curriculum, there must be a sufficient number of faculty members with documented qualifications to instruct and adequately supervise all anesthesia fellows in the program. Although the number of faculty members involved in teaching will vary, there should be at least three and these should be equal to or greater than two full-time equivalents, including the program director. A ratio of no less than one full-time equivalent faculty member to one subspecialty fellow must be maintained. The anesthesia faculty must possess the requisite congenital cardiac anesthesia specialty expertise, competence in clinical care, and teaching abilities, as well as documented educational and administrative abilities and experience in their field. There must be evidence of active participation by qualified physicians with training and/or expertise in congenital cardiac anesthesiology beyond the requirement for completion of a core anesthesiology residency. The faculty members should have training and experience that would generally meet or exceed that associated with the completion of a 1-year congenital cardiac anesthesiology program. Faculty members in cardiology, cardiothoracic surgery, pediatrics, intensive care, and pulmonary medicine can provide teaching in multidisciplinary conferences. The responsibility for establishing and maintaining an environment of inquiry and scholarship of discovery, dissemination, and application rests with the program director and the faculty, and an active research component must be included in each program.

Equally important to recruiting qualified faculty members with the appropriate expertise and training in congenital cardiac anesthesiology is developing their ability to teach the curriculum. It is a common error to assume that faculty members with the necessary clinical skills, knowledge, and specialty expertise are also qualified to teach. Rarely are they required to provide documentation of their teaching experience or evidence of teacher training, even for the most basic skills such as assessing and providing feedback to learners, leaving many ill-prepared for their teaching responsibilities. The core components of a faculty development program in training congenital cardiac anesthesiology fellows should include:

- Communication of curricular goals and objectives
- Discussion of qualities that characterize effective and respected clinical educators
- Suggestions of how to apply adult learning principles to congenital cardiac anesthesia clinical venues
- Assurance that faculty members can effectively assess trainees and provide useful feedback on their performance
- Review of best teaching practices for common educational strategies such as procedural teaching as well as large and small group facilitation skills
- Specialized training sessions to teach faculty members how to communicate and explain clinical decision-making; make teaching in the OR a priority; maintain a balance between supervision and autonomy; promote critical thinking skills; and provide clear, constructive, and developmental feedback.

**Evaluation and feedback**

Evaluation and feedback are essential for the continuous improvement and development of a curriculum. The purpose of evaluation in medical education is to determine if the curricular goals and objectives were met. In addition, an evaluation can determine if the time, resources, and effort spent producing the curriculum are merited. Evaluation results can be used to identify educational outcomes, assess teaching effectiveness, determine areas of strength and needed improvement, and make decisions about the
level of support necessary to sustain or further develop a curriculum. “Feedback” is defined as the provision of information regarding an individual’s or program’s performance to trainees, faculty, stakeholders, and accrediting agencies. While the terms “evaluation” and “assessment” are often used interchangeably when measuring both individual learner and program outcomes, it is best to distinguish between them, adopting the term “evaluation” in relation to measurement of the curriculum, and “assessment” in relation to the measurement of learners. As learner assessment often comprises a significant portion of a program’s evaluation, making this distinction will help to avoid confusion when planning and presenting results [28].

The process of curriculum evaluation and feedback

To conduct a comprehensive evaluation of a congenital cardiac anesthesiology program, multiple sources of data must be sought, which requires a systematic information collection process involving learners, faculty, other healthcare providers, and, in some cases, external evaluators. Data and information should be collected at the start of a curriculum, and also at its midpoint, conclusion, and subsequent to completion (e.g. 6–12 months post-fellowship). A program director’s effort in collecting evaluation data at the program’s mid- and endpoints will be less challenging if the requisite time and effort are put into creating specific and measurable learning objectives at the start of a curriculum, and into assessing the fellows’ knowledge, skills, and performance levels in congenital cardiac anesthesia up-front. With the appropriate administrative support, a program director can institute an iterative “plan–do–check–act” methodological approach to continuous curriculum improvement. This method involves planning (the curriculum development steps 1 through 4 – problem identification through educational strategies); doing (the implementation step); checking, in which data are collected to determine what is going well and what needs to be improved moving forward; and acting, in which the program director addresses identified curricular problems by determining their causes and applying countermeasures, standardizes what is working well, and communicates decisions, new standards and improvements to be made.

Kirkpatrick described four levels to focus program evaluation, which Curran and Fleet later adapted for use in medical education evaluation:

- **Reaction** – this level of evaluation is intended to evaluate how well participants liked a program. It generally provides data concerning participants’ perceptions, and satisfaction with objectives, content, instruction, delivery, and/or instructors.
- **Learning outcomes** – this level of evaluation involves some form of assessment of changes in skills, knowledge, or attitudes among learners; it is most commonly conducted through pre- and post-test study designs.
- **Performance improvement** – this level of evaluation provides information on the extent to which learning has influenced the post-learning behavior or performance of learners in their practice setting. Evaluating at this level attempts to answer the question: Are the newly acquired skills, knowledge, or attitudes being used in the everyday environment of the learner?
- **Patient/health outcomes** – this level of evaluation is concerned with measuring tangible results which are influenced by the performance of the learner as a result of participation in the education activity. These tangible results can be transferred to a health perspective (e.g. improving patient health or improving efficiencies). Evaluation at this level is challenging given the variety of uncontrollable variables a learner encounters when he or she leaves an educational program.

A program director needs first to determine the intention of the curriculum evaluation as well as the audience reviewing the results in order to choose which level(s) to focus his or her time and effort on. For example, if a department chair is mostly interested in whether the fellows are better able to perform advanced TEE in the OR, then evaluation results should report on learning outcomes. If, however, the Vice President of Healthcare Quality is interested to report to the board on the reduction of anesthesia-related complications post-CHD surgery, then the focus should be on patient/health outcomes.

Learner assessment methods

With the adoption of outcomes-based training requirements in 2002, the focus of learner assessment for all residency programs has been on the ACGME’s six core competencies. The goal of competency-based assessment is for trainees to meet discreet, transparent, achievable objectives at developmentally appropriate stages in training. The challenge for program directors of congenital cardiac anesthesiology training programs is to ensure that the curriculum’s goals and objectives match the intended competencies. As Ebert and Fox [33] note:

“To establish competence in congenital cardiac anesthesia could mean standardized classroom teaching, followed by defined experiences in the clinical setting. For example: The fellow’s progression of skills and knowledge of TEE, aortic balloon pumps, left ventricular assist devices, on-and-off pump procedures, management of hemodynamics in patients with complex valve abnormalities, right heart failure, pulmonary hypertension, and significant arrhythmias would be carefully structured. If the opportunity did not present itself in the clinical setting, high-fidelity simulation could fill the gap. This type of competency-based teaching and learning could assure that a fellow from any program would have a consistent, comparable, and meaningful experience in the specialized field of congenital cardiac anesthesia. The same would need to be developed for all learning areas within anesthesiology.”
Learner assessment should be thought of in terms of formative and summative purposes. Formative assessment should be provided consistently throughout a fellowship program, as it provides trainees with feedback on their performance towards defined educational objectives. It also steers learning towards desired outcomes, and can focus high-achieving learners towards more rapid skill advancement. Summative assessment determines how well learners achieved competency of specific objectives at developmentally appropriate stages in their training. These are conducted at the end of a rotation or program.

For formative and summative learner assessment to be considered reliable, performance data must be obtained from the predominant clinical units where congenital cardiac anesthesia trainees work and learn. Multidisciplinary cardiothoracic team members, including supervising anesthesiologists, surgeons, nurses, and other staff members in the OR or ICUs, should use multiple assessment methods and tools (e.g., standardized checklists, performance audits, case logs), in combination with the trainee’s own self-assessment, to create a comprehensive performance appraisal system required in a competency-based training model.

Learner assessment methods can be categorized as cognitive, affective, or psychomotor appraisals. Cognitive learner assessment methods are used to determine and provide feedback about trainees’ acquisition and application of biomedical, clinical, epidemiological, and social behavioral sciences knowledge, as well as their ability to problem-solve, reason through clinical challenges, and use critical thinking skills. Methods include:
- Written or computer-interactive tests – multiple choice, essay-type questions
- Oral examinations
- Questionnaires
- Individual interviews
- Procedural, operative or case logs
- Chart stimulated recall
- Review of scholarly projects and research
- Observation of a fellow’s ability to apply data from advanced monitoring devices.

Affective learner assessment methods are used to appraise and provided feedback about trainees’ attitudes, feelings, motivations, and decisions. Methods include:
- Standardized patient exercises
- Questionnaires
- Written reflections and essays
- Rating and forced ranking forms
- Patient and family surveys
- Teamwork exercises
- Peer assessment of professionalism
- Case-based discussions that involve clinical uncertainty or ethical dilemmas
- Individual interviews
- Self-report of adverse events and near misses related to pediatric cardiothoracic and vascular anesthesia rotations
- Root cause analyses of medical errors or complications of patients under the fellows’ care.

Psychomotor learner assessment methods are used to appraise and provide feedback on trainees’ physical skills or the performance of actions. There are numerous methods to use for psychomotor assessment. Methods must be criterion-based, anchored using demonstrable behaviors, and developmentally appropriate. The most common methods are:
- Simulation exercises
- Portfolios of videotapes
- Direct observation of discrete procedural skills (such as intubation or line placement)
- Objective structured clinical examinations
- Objective structured assessment of technical skills
- Mini-clinical evaluation exercise
- Clinical encounter cards
- Clinical work sampling
- Practice metrics scoring using data collected as part of routine care via an existing perioperative information management system (e.g. central line insertion and temperature management).

The assessment process for congenital cardiac anesthesia trainees should emphasize learning, inspire confidence in the trainee, enhance the trainee’s ability to self-monitor, and drive the institutions toward self-assessment and curricular change when necessary. The primary endpoint should be the ability to demonstrate trainee competence in the care of their patients in accordance with the ACGME’s six core competencies – patient care, medical knowledge, systems-based practice, professionalism, interpersonal and communication skills, and practice-based learning and improvement.

In 2014, all anesthesiology residency programs will enter the ACGME’s Next Accreditation System. A major aspect of this system involves the creation of roughly 30 milestones for each specialty that will map to different areas within the construct of the six core competencies. Milestones are “specialty specific achievements that residents are expected to demonstrate at established intervals as they progress through training” [38]. While it is not within the purview of this chapter to expound upon the anesthesiology residency milestones in detail, nor have milestones for anesthesiology specialty training been established, the reader is directed to the “The Anesthesiology Milestone Project,” a joint initiative of the Accreditation Council for Graduate Medical Education and The American Board of Anesthesiology at http://www.acgme.org/acgmeweb/Portals/0/PDFs/Milestones/AnesthesiologyMilestones.pdf.

Program evaluation methods
Curriculum developers perform evaluation of an educational program to make judgments about its successes and deficiencies; decide about resource allocation, administrative support, and material management; determine teaching performance; uncover influencing attitudes regarding the curriculum’s educational value; pinpoint
areas that are effective and that are in need of improvement; and conclude whether the curriculum met its intended learning goals and objectives and should continue to be incorporated into a training program.

A core component of the program evaluation process is to conduct and collect data from formative and summative learner assessment methods. The faculty must evaluate in a timely manner the fellows whom they supervise. In addition, the fellowship program must demonstrate that it has an effective mechanism for assessing fellow performance throughout the program and utilizes the results to improve fellow performance. At a minimum, faculty members responsible for teaching must provide critical assessment of the six ACGME core competences for each fellow at the end of 6 and 12 months of training. Learner assessment should include regular and timely performance feedback to fellows that includes at least semi-annual written evaluations. Such evaluations should be communicated to each fellow in a timely manner and be maintained in a record that is accessible to each fellow. The program director or designee must inform each fellow of the results of the evaluations at least every 6 months during training, advise the fellow of areas needing improvement, and document the communication. Assessments should include the fellows’ fund of knowledge, clinical judgment and clinical psychomotor skills, patient management skills, and ability to critically analyze complex clinical situations. Periodic evaluation of patient safety and teamwork is mandatory. Evidence of the congenital cardiac anesthesiology fellows’ scholarly projects and research, including those pertaining to continuous quality improvement and risk management, should be reviewed and summarized by designated faculty mentors.

The program director should conduct a final evaluation for each fellow who completes the program. This evaluation must include a review of the fellow’s performance during the final period of education and should verify that the fellow has demonstrated sufficient professional ability to practice competently and independently. Documentation of the congenital cardiac anesthesiology fellows’ successful completion of the program as well as subsequent training or career plans should be kept up-to-date, as this information will help to inform future program evaluation efforts. A program director should also maintain a listing of all graduating fellows’ scholarly activities as well as aggregate feedback from the ACGME’s Resident-Fellow Surveys. This survey provides feedback on duty hours, faculty supervision and instruction, fellow evaluation processes, educational content and resources, patient safety and teamwork, as well as overall reflections on the quality of the training program.

**Faculty members**

As part of a comprehensive curriculum evaluation effort, faculty members should be evaluated on their congenital cardiac anesthesia teaching performance and supervisory capabilities. Clinical teaching assessment instruments should produce valid and reliable results and any findings should be provided to faculty members in a clear and concise format. The faculty members should be assessed on their medical knowledge, clinical competence, teaching effectiveness, scholarly activities, and professional attributes. Lombarts et al. found that existing tools can be adapted for the systematic evaluation and support of faculty members involved in residency programs. They suggest basing faculty evaluation on qualities established by the well-known Stanford Faculty Development Program instrument. These qualities include establishment of an effective learning climate, professional attitudes towards trainees, communication of goals, evaluation of trainees, and quality of feedback provided. Moreover, Baker’s study of resident assessment of educators in anesthesiology provides data about the positive impact that trainee evaluation can have in motivating clinicians to become better teachers [41].

**Overall program effectiveness**

Summative program evaluation provides information on the degree to which a curriculum has met its intended objectives and at what cost. It can also document the curriculum’s success in engaging and motivating its learners and faculty as well as associated subspecialty anesthesiology training programs. In addition to quantitative data, summative program evaluation may include qualitative information about educational barriers and unanticipated obstacles as well as means to streamline curriculum implementation. The results of summative program evaluations are often disseminated to stakeholders to obtain or maintain time, administrative support, funding, and other resources. The educational effectiveness of a program must be evaluated at least annually in a systematic manner.

Representative program personnel (at a minimum the program director, representative faculty, and one fellow) must be organized annually to review program goals and objectives, and the effectiveness with which they are achieved. In the evaluation process, the group must take into consideration written comments from the faculty, the most recent report of the graduate medical education committee of the sponsoring institution, and the fellows’ confidential written evaluations. If deficiencies are found, the group should prepare an explicit plan of action, which should be approved by the faculty and documented in the minutes of the meeting.

The program should use fellow performance and outcome assessment in its evaluation of the educational effectiveness of the fellowship program. Performance of program graduates in the certification examination should be used as one measure of evaluating program effectiveness. The program should maintain a process for using assessment results together with other program evaluation results to improve the fellowship program.
**Curriculum maintenance and enhancement**

Once a curriculum in congenital cardiac anesthesia has been developed, the next challenge is curriculum maintenance. A successful curriculum is continually developing by responding “to evaluation results and feedback, to changes in knowledge base and the material requiring mastery, to changes in resources (including faculty), to changes in its targeted learners, and to changes in institutional and societal values and needs”. Areas for curricular enhancement may include review of the written or intended curriculum, assessment of the environment/setting of the curriculum, and determination of learner assessment methods to meet new accrediting agency requirements (such as the ACGME’s milestones). The following data can be collected and utilized to assess how well a curriculum is functioning:

- Program evaluation
- Learner/faculty/patient questionnaires
- Patient quality metrics
- Objective measures of learners’ skills and performance
- Focus group of learners, faculty, staff, and patients
- Other systematically collected data
- Regular/periodic meetings with learners and faculty
- Special retreats and strategic planning sessions
- Site visits
- Informal observation of curricular components, learners, faculty, and staff
- Informal discussions with learners, faculty, and staff

Congenital cardiac anesthesia is a subspecialty in which there are significant interactions between anesthesiologists and cardiac surgeons, cardiologists, radiologists, and other pediatric subspecialists. Close alliance between these disciplines is vital to the growth and development of the subspecialty. Furthermore, curriculum enrichment is dependent on both intra- and inter-subspecialty collaboration as well as combined faculty development efforts.

**Dissemination**

There is a need for an international comprehensive curriculum in congenital cardiac anesthesia. Local adaptation of a core curriculum will be necessary to overcome technological and cultural care delivery obstacles. The following issues should be considered when considering dissemination of core curriculum material:

- What material should be disseminated?
- How should the material be disseminated (publications, presentations, multi-institutional interest groups or academic societies, educational clearinghouses, online learning systems, digital communication, instructional videotapes or audiotapes, and/or instructional computer software)?
- What resources are required (time and effort, personnel, equipment/facilities, funds)?
- How can dissemination and impact be measured?

Dissemination of a curriculum can be a valuable process, benefiting many other congenital cardiac anesthesia trainees. A coherent strategy must be determined on what should be disseminated, appropriate methods of dissemination, and the best use of limited time and administrative resources.

**Role of professional societies**

At present, the CCAS, in conjunction with the Society of Pediatric Anesthesia (SPA), has taken the lead in developing a core curriculum for fellowship training in congenital cardiac anesthesia. Close future collaboration with the Society of Cardiovascular Anesthesiologists (SCA) will be necessary. The ACGME has revised the case requirements for the adult cardiothoracic anesthesiology fellowship in 2014 and has not mandated any case requirements at this time. Collaboration with the ACGME, RRC, and the American Board of Anesthesiology will be necessary as the subspecialty matures to the point where it becomes a board certifiable specialty in its own right. As many children with CHD survive to adulthood and develop adult cardiothoracic disease, the American Heart Association as well as the American College of Cardiology may be able to provide significant input into developing a holistic approach to the care of this complex patient population. A significant proportion will go on to become pregnant and hence both the American College of Obstetricians and the Society for Obstetric Anesthesia and Perinatology will need to contribute to the development of a curriculum.

**Conclusion**

Developing durable new curricula will be challenging in the highly specialized area of congenital cardiac anesthesia. Use of a systematic approach to its development will facilitate efficient teaching and learning in this complex discipline. It is important to develop programs that give faculty members the necessary skills to develop curricula and that provide mentoring. Finally, the challenge of transitioning trainees from fellow (learner) to faculty member (provider and teacher) in congenital cardiac anesthesia will be ongoing. Radical and creative changes in the existing method of instruction in congenital cardiac anesthesia are required to produce well trained additions to our profession. It is increasingly difficult to achieve, in a competitive clinical environment, clinical competency based on the traditional apprenticeship model, and hence the best method to achieve competency in our learners is yet to be determined. Trainees should be encouraged to create a learning portfolio, preferably web-based, that is a record of participation and achievement, career goals and professional development, physical evidence, and reflective writing.
Selected References
A full reference list for this chapter is available at:
http://www.wiley.com/go/andropoulos/congenitalheart

1 DiNardo JA, Andropoulos DB, Baum VC. Special article: a proposal for training in pediatric cardiac anesthesia. Anesth Analg 2010;110:1121–5. Despite a relatively universally applicable knowledge base and skill set, training and experience in pediatric cardiac anesthesia in currently organized basic anesthesia and adult cardiothoracic anesthesia fellowship programs are very limited and not uniformly available. The authors present a schema, developed by a working group of the CCAS, for training in pediatric cardiac anesthesia that should be considered by pediatric cardiac anesthesia educators internationally as a template to be modified as necessary.


9 Kern DE, Thomas PA, Hughes MT. Curriculum Development for Medical Education: A Six-Step Approach, 2nd edn. Baltimore, MD: The Johns Hopkins University Press, 2009. This is an excellent resource published by the faculty at Johns Hopkins University, discussing the different steps involved in new curriculum development. Problem identification and general needs assessment. Targeted needs assessment, goals and objectives, educational strategies, implementation, evaluation and feedback are discussed in detail.

13 Wong A. Review article: teaching, learning, and the pursuit of excellence in anesthesia education. Can J Anesth (2012); 59:171–81. Excellent teaching is considered that which facilitates and maximizes learning. A conceptual framework of learning as a convergence of teacher, learner, assessment, and context is proposed in this article. The contribution of each component to learning is examined in order to enable anesthesia teachers to choose and adapt the most appropriate educational approaches for their particular contexts.

23 Lorello GR, Cook DA, Johnson RL, Brydges R. Simulation-based training in anaesthesiology: a systematic review and meta-analysis. Br J Anaesth 2014;112:231–45. Using meta-analysis and critical narrative analysis, the authors synthesized the evidence for the effectiveness of simulation-based anaesthesiology training. Their critical analysis showed inconsistency in the measurement of non-technical skills and consistency in the (ineffective) design of debriefing. Simulation in anaesthesiology appears to be more effective than no intervention (except for patient outcomes) and non-inferior to non-simulation instruction.


28 Cook DA. Twelve tips for evaluating educational programs. Med Teacher 2010;32:296–301. This article helps educators to evaluate an educational program to determine its merit or worth. The two most important questions in any evaluation are, ‘Whose opinion matters?’ and ‘What would really be meaningful to them?’

33 Ebert TJ, Fox CA. Competency-based education in anesthesia: history and challenges. Anesthesiology 2014;120:24–31. The Accreditation Council for Graduate Medical Education is transitioning to a competency-based system with milestones to measure progress and define success of residents. Curriculum must be redesigned and assessments will need to be precise and in-depth.

38 Nasca TJ, Philibert I, Brigham T, Flynn TC. The next GME accreditation system – rationale and benefits. New Engl J Med 2012;366:1051–6. This article discusses the merits and work that need to be done in the creation of the Next Accreditation System (NAS). Key benefits of the NAS include the creation of a national framework for assessment that includes comparison data, reduction in the burden associated with the current process-based accreditation system, the opportunity for residents to learn in innovative programs, and enhanced resident education in quality, patient safety, and the new competencies.

41 Baker K. Clinical teaching improves with resident evaluation and feedback. Anesthesiology 2010;113:693–703. This study sought to determine whether resident-provided numerical evaluation and written feedback to clinical teachers improved clinical teaching scores. A combination of evaluation and feedback, including comments on areas for improvement, was related to a substantial improvement in teaching scores.
CHAPTER 3
Quality, Outcomes, and Databases in Congenital Cardiac Anesthesia

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Introduction

Patient safety in the operating room (OR) and beyond has long been a driving force in anesthesia care. Technical innovations such as pulse oximetry and capnography, combined with better trainee and practitioner education, have dramatically increased safety for our patients and the quality of our anesthesia care. Additionally, newer medications, technologies and monitoring modalities continue to advance the field. As a result of these systemic changes, anesthesia-related patient morbidity and mortality have steadily declined across all patient populations. Non-technical attempts to reduce perioperative complications have become another major focus of various organizations such as the World Health Organization (WHO) and the Joint Commission for the Accreditation of Hospital Organizations (JCAHO). Efforts to delineate the frequency of complications related to anesthesia in patients undergoing congenital cardiac surgery and procedures in the cardiac catheterization laboratory and elsewhere have been difficult, because of the low occurrence of this surgery compared with other surgeries on children and the relatively rare incidence of anesthesia-related complications. Busy cardiac anesthesia services at major North American pediatric institutions will each only have contact with 2,000–3,000 congenital cardiac patients per year and the majority of these cases are non-surgical, such as diagnostic and therapeutic catheterizations and radiology procedures. The recognition of the need to systematically quantify and study outcomes in pediatric cardiac surgery, anesthesiology, and catheterization has led to several multi-institutional and multinational efforts to organize large databases over the past two decades.

This chapter begins with a discussion of errors and outcomes in surgery and anesthesia, emphasizing communication and teamwork. Next, systems for prospective risk assessment in pediatric cardiac surgery are discussed. Then, an analysis of closed malpractice claims in anesthesia is presented, and subsequently a discussion focusing on pediatric cardiac anesthesia morbidity and mortality. Finally, database initiatives in congenital cardiac anesthesia, surgery, and interventional catheterization are presented.

Errors and outcomes in surgery and anesthesia

The perioperative management of patients with congenital heart disease (CHD) is fraught and there are occasions when even small decision-making errors can have catastrophic outcomes. James Reason has described the “Swiss cheese model” for evaluating patient complications due to human errors [1]. For a complication to occur, all the “holes” in the cheese have to line up – that is, there is a sequential failure of various defense mechanisms in place.
to prevent, recognize and/or treat unwanted physiologic changes (Figure 3.1). Many “anesthesia” complications are multifactorial in origin and it can be difficult to assign the relative contributions of different clinical services. For example, failure to successfully separate from cardiopulmonary bypass may be due to issues such as technical difficulty or bleeding (surgery), inotrope management (anesthesia and surgery), ventilator management (anesthesia), or underlying patient physiology such as intractable pulmonary hypertension. These system factors are further exacerbated if there are communication difficulties between the various parties, including surgeons, anesthesiologists, perfusionists, cardiologists, and the pre-and postoperative medical and nursing teams [2].

de Leval and colleagues investigated the impact of human factors and teams on surgical outcomes in congenital cardiac patients, focusing on the neonatal arterial switch operation (ASO) as a marker for complex, high-risk surgery [3]. Patient and procedural data were collected on 243 operations performed by 21 cardiac surgeons in the United Kingdom in 16 centers over 18 months. Of these 243 patients, case study data were collected on 173 ASOs by two human factors researchers who followed each case from the time of induction of anesthesia until care was transferred to the intensive care team. The observed adverse events were subsequently divided into major and minor events depending on their impact on the safety of the patient. Analyses determined that, after adjustment for patient factors, the total number of minor and major events per case were both strong predictors of the probability of death and near-miss events for major morbidity or death ($P < 0.001$). The authors concluded that minor events go largely unnoticed by the OR team and are therefore left uncompensated. A subsequent examination of the same data suggests that minor events impede the OR team’s ability to compensate for future major events [4].

In addition to the organizational factors, pediatric cardiac surgery procedures have a low error tolerance. The Bristol Royal Infirmary Inquiry and the Manitoba Inquiry reports both recognized the importance of human factors and systems research in improving pediatric cardiac surgical outcomes [5,6]. The report of the Manitoba Pediatric Cardiac Surgery Inquest found that “serious organizational and personnel problems experienced by the Health Sciences Center’s Pediatric Cardiac Surgery Program during 1993 and throughout 1994 contributed to the deaths of these children.”

Galvan et al. published an observational study on complications in this complex patient population and recorded on average 1.8 major compensated and nine minor compensated complications per case [7]. These complications were observed during the surgeries but were all recognized and treated by the medical team before injury resulted – all the “holes” in the Swiss cheese did not line up because one or more of the various systems in place to prevent patient injury worked appropriately. Barach et al. reported on a comprehensive process map in which they outlined the multiple steps involved in congenital cardiac anesthetic care and identified the potential sites for safety interventions [8]. They observed 108 open cardiac surgeries and found that communication failures were the most common underlying cause of major events. Examples of the organizational and human factors challenges that Barach et al. observed include:

- Unplanned transfusion of blood products correlated with a breakdown of communication between the anesthesia team, the nurses and the perfusionist.
- Failure to identify a non-functioning infusion pump was directly related to poor communication between the anesthesia attending physician and the resident who was performing several tasks simultaneously.
- Detection of increased chest tube bleeding was delayed and may have been related to suboptimal communication between residents and the attending physician.

“Near misses” are important as they are 10–100 times more common than documented adverse events and yet share the same organizational and cognitive sources of error as major adverse events. Determining the frequency and nature of “near miss” events is potentially far more important than just looking at system failures resulting in patient injury. However, “near miss” analysis is difficult as it requires a trained, independent observer to accompany the patient through the entire care continuum.

Outcome transparency has become a key component of programmatic evaluation. For example, news articles have disclosed congenital cardiac surgical program closures possibly related to adverse patient outcomes compared with their cohorts, while other institutions have made the decision to publicly release their pediatric heart surgery outcome data on a regular basis in an attempt to provide the most accurate data possible [9–11]. Although there is currently no mandatory reporting for congenital cardiac surgical or anesthesia programs nationwide, the Society of Thoracic Surgeons (STS) has begun providing “star” ratings on its website for adult heart surgery outcomes in isolated coronary artery bypass grafting or aortic valve replacement operations [12]. In Great Britain, congenital cardiac program mortality is reported publicly for all programs through the Central Cardiac Audit Database [13]. To date, there has been no similar effort to publish anesthesia morbidity and mortality, both because it is
so infrequent and because of the absence of a national clearinghouse.

**KEY POINTS: ERRORS AND OUTCOMES IN SURGERY AND ANESTHESIA**

- Reason’s Swiss cheese model has been widely cited in explaining patient complications in complex systems.
- The total number of minor and major adverse events during complex congenital heart surgery were strong predictors of morbidity and mortality in de Leval’s study.
- “Near-miss” events are 10–100 times more common than adverse events yet they share the same sources of error.

**The six “Cs”: communication and teamwork**

In complex environments like pediatric cardiac ORs or catheterization laboratories, errors cannot and will not be avoided or eliminated. In his publication *Normal Accidents: Living With High-risk Technologies*, Perrow has postulated that even the best teams cannot eliminate every error [14]. What they can achieve at best is to prolong the time interval between errors. Therefore, it is of great importance for successful hospitals to create a culture of safety similar to the culture that the aviation industry promulgated to minimize the risk of human errors. More than a decade was required before hospitals were able to embed the concepts of checklists, team time-outs and sign in/sign out procedures as components of daily safety procedures. In commercial aviation, one must realize that computers in modern airplanes have taken over the human function of checking lists. These computers are checking the lists themselves automatically, because analysis of the human practice of using a checklist a hundred times reveals that this is a source of error in itself. The effort in the aviation industry now is more focused on team performance, simulation, and reducing errors due to hierarchy and authority issues. The six “Cs” – communication, cooperation, coordination, cognition (simulation and cross-training), conflict (managing disruptive behavior) and coaching (team-training) – are the key goals for successful working interdisciplinary teams. A comprehensive summary of this topic is presented by Wahr et al. [15].

The JCAHO and WHO have both advocated instituting a time-out system prior to procedures to minimize the risk of preventable complications such as wrong-site surgery and failure to administer antibiotics in a timely manner [16]. In addition, “closed-loop” communication has been encouraged to minimize system errors. (Figure 3.2) [17]. This particular technique is very helpful in the OR environment, where there can be a wide variety of distractions from background noise, cellular telephones, computers, monitors, conversations and alarms. Shaw and Stayer recently reviewed much of this literature in their chapter, “Operating room safety, communication and teamwork” in the most recent edition of *Gregory’s Pediatric Anesthesia* [18]. There are a variety of additional techniques to maximize communication in the OR (or any other procedural location) as well as documenting the flow patterns that may lead to adverse events [16].

**KEY POINTS: COMMUNICATION AND TEAMWORK**

- Communication, cooperation, coordination, cognition, conflict management, and coaching are key goals for interdisciplinary teams.
- Checklists and timeout procedures are now accepted as mandatory components of complex systems such as congenital cardiac surgery.
- Closed-loop communication is an accepted strategy to minimize system errors.

**Databases in pediatric cardiac surgery and anesthesiology**

In order to better quantify both the incidence of adverse events and the outcomes of surgical procedures, in the 1990s the STS database committee established a nationwide (and now international) voluntary and anonymous registry of congenital cardiac cases and outcomes [19]. Of the 117 locations in the US and eight locations in Canada that provided surgical care for congenital cardiac lesions in 2013, the database had 112 centers submitting their information during the annual data harvest. This included almost every congenital cardiac center in the US (108 sites...
out of 117) and four outside of the US (three in Canada and one in Japan). As of the Fall 2013 report, the STS Congenital Heart Surgery Database (STS-CHSD) held information on over 292,828 patient surgical procedures, more than half of which took place within the past 5 years. The European Association for Cardio-Thoracic Surgery (EACTS) has developed a transnational system for congenital cardiac surgery throughout the European continent and the UK. The EACTS utilizes a shared nomenclature for both lesions and complications with the STS that allows pooling of the two data sets to create an even larger picture of worldwide congenital cardiac surgery and outcomes.

These data serve as an important resource for determining nationwide outcomes on a given congenital cardiac lesion and benchmarks by which individual hospitals and surgeons can compare their results against aggregate results on a lesion-by-lesion, complexity, and age-adjusted basis. Both public and private payers have begun to incorporate these data in evaluating programs. The state of Florida, for example, has mandated participation in this type of database as a requirement for participation in state-run insurance programs such as Medicaid [20]. In New York state, the Department of Health publishes outcomes data on every program in the state, including whether they fall above or below 95% confidence intervals for expected outcomes after risk adjustment [21]. The private health insurer United Healthcare has established “centers of excellence” to facilitate referrals within their systems and to maximize their patient outcomes and satisfaction while minimizing the added expense of complications [22,23]. Demonstration of superior outcomes through benchmarking is one element of the requirements for consideration as a preferred referral center, and the popular US News and World Report Hospital and Specialty annual rankings include database participation and benchmarking in their ranking algorithm [24].

Other important efforts that have come out of the STS-CHSD include working groups that have established the consensus guidelines for defining lesion nomenclature, morbidity, and mortality [25]. All of these efforts have been coordinated internationally with other groups such as the EACTS to allow the free flow of comparative data across national boundaries. Additionally, work is ongoing to span specialties to involve pediatric cardiology, cardiac anesthesia, intensive care, and governmental agencies.

A well-recognized weakness of the current single-site reporting system is that a patient undergoing a procedure at one institution may suffer an adverse event that requires transfer to another institution. In the case of an adverse event, the latter facility becomes the center that reports the morbidity in their statistics, while the initial treating institution does not report the event. Efforts are underway to include incorporating state and national death indices to track patient mortality beyond the initial postoperative period and capture mortality information on patients lost to follow-up. Participant groups are also trying to develop US Health Insurance Portability and Accountability Act-compliant mechanisms for identifying individual patients as they move through their care at multiple institutions.

The Congenital Cardiac Anesthesia Society (CCAS) was incorporated in 2005 and one of its first initiatives was to approach the STS about developing anesthesia information to be included in the STS data set [26]. The STS has been very supportive of this collaboration and sees it as a model for future incorporation of additional specialties that share the same patients, such as pediatric interventional cardiology and pediatric cardiac critical care medicine. The CCAS work with the STS served as a model for the Society of Cardiovascular Anesthesiologists (SCA) Adult Cardiothoracic Anesthesia Database, which is now working in conjuction with the appropriate STS data set. The adult SCA database began entering patient data in 2013 and tends to focus more on echocardiographic findings rather than outcomes or adverse events [27].

A major benefit of utilizing an annual data submission process across multiple institutions is that it allows for a far more contemporaneous examination of patient outcomes. Publications from two centers with a long history of anesthesia data collection, the Boston Children’s Hospital and the Mayo Clinic, illustrate the difficulties with single-center record-keeping [28,29]. Their data, critically important as it is, represents time periods ranging from 6 years (Boston) to 17 years (Mayo). During these time spans multiple factors may shift that significantly alter patient outcomes and potential complications. For example, personnel changes and experience (physician, nursing and ancillary staff), surgical technique modifications, pharmacology, technical advances with better monitoring and equipment, and more sophisticated complication detection and tracking all impact patient outcome statistics. In examining low-frequency events, the only way in which to properly determine their occurrence is to investigate large numbers of patients. As no single center can provide sufficient patients as a denominator in a short period of time, it is necessary to either lengthen the epoch studied (with the weaknesses mentioned earlier) or increase the denominator by expanding the patient base by making the data multi-institutional. One goal of the STS–CCAS collaboration is specifically to do the latter.

**KEY POINTS: DATABASES IN PEDIATRIC CARDIAC SURGERY AND ANESTHESIOLOGY**

- The STS Congenital Heart Surgery Database was the first multi-institutional effort to gather data on practice and outcomes.
- The EACTS has also developed a similar database for congenital heart surgery.
- Cardiac anesthesia databases have been initiated by the CCAS and the SCA, appended to the surgical databases.
Prospective risk assessment in pediatric cardiac surgery and cardiology

It is intuitive that different pediatric cardiac surgical procedures will have radically different long-term outcomes related to the underlying severity of the defect, the complexity of the operative repair, and the co-morbidities found in a given patient. In order to best estimate these potential outcomes, initial efforts were made at developing risk categories based upon “best guess” techniques in which groups of cardiac surgeons and cardiologists essentially sat down in a room and assigned each individual operative procedure to a risk category pool based upon their collective years of experience. The most widely adopted categorization schema utilizing this technique is the Risk Adjustment for Congenital Heart Surgery (RACHS-1) scoring system developed by Jenkins and colleagues [30,31]. The Aristotle Basic Complexity (ABC) score is another popular method of preoperative risk assessment utilizing expert consensus based upon values being assigned to three components: the potential for perioperative mortality, the potential for perioperative morbidity, and the technical difficulty of the proposed repair [32]. The ABC system expanded the number of procedures evaluated, as compared with the RACHS-1 system, but the RACHS-1 appears to better discriminate at predicting mortality when the two are compared against each other [33]. The weakness of both of these systems is that they are based upon a consensus estimation of experts in the field. The STS, in conjunction with the EACTS, subsequently developed a risk model developed from empirical outcome data from the two database groups, the Society of Thoracic Surgeons–European Association for Cardio-Thoracic Surgery Congenital Heart Surgery (STAT) mortality score. The STAT score was modeled utilizing over 70,000 records from the two societies and divides pediatric cardiac surgical procedures into five levels of mortality categories (“strata”); however, these are based upon the observed outcomes rather than a priori assignment by expert opinion and this process was then validated by comparison to a larger sample set of over 111,000 pediatric cardiac surgical cases in both the STS and EACTS registries [34]. Each mortality category was created so that the inter-category differences were sufficient to warrant assignment to either a lesser or a greater score category. Table 3.1 contains a listing of the STAT assigned procedures and their respective categories. The STAT, RACHS-1 and ABC scores are all based upon in-hospital mortality rates and do not fully account for either in-hospital morbidity or out-of-hospital mortality, such as inter-stage deaths that occur after discharge. Another major component that is not accounted for in these systems is morbidity, such as prematurity, genetic abnormalities, or co-existing diseases. Work is progressing on each of these issues as they relate to patient outcomes.

Pasquali et al. have drawn extensively from work done in adult cardiovascular surgery to determine the relevance of “failure to resuscitate” (FTR) as a marker for programmatic quality [35]. The authors start with the hypothesis that complications and morbidity will always occur in any complex system such as the surgical repair of congenital heart defects. A recent single-site retrospective analysis by Agarwal and colleagues found an incidence of identified adverse events of 43% (126 of 325 patients); this was in a retrospective chart review, not in the type of prospective observational study performed years earlier by de Laval and Barach, which might identify more subtle minor events that occur without being recorded [3,8,36]. What distinguishes high-performing programs from lesser-performing ones is not the incidence of adverse events per se, but the response to them.

Interventional cardiologists have also recently addressed predictive outcomes analysis. Bergersen et al. prospectively collected data from eight sites participating in the Congenital Cardiac Catheterization Project on Outcomes (C3PO) registry utilizing a web-based tool on all cardiac catheterization cases [37]. Post hoc analyses utilizing multivariate modeling then determined four discrete procedural risk categories based upon the age of the patient and the type of procedure being performed (diagnostic, valvuloplasty, device or coil closure, angioplasty, stent placement, stent redilation, and other). Adverse events were categorized on a scale of 1–5, with 1 being no adverse event noted, and 5 catastrophic (i.e., resulting in death or emergent surgical intervention to prevent death). The risk scoring method was called the Catheterization for Congenital Heart Disease Adjustment for Risk Method (CHARM). The purpose of the C3PO and CHARM project is to allow for appropriate risk adjustments to be made when comparing outcomes at a given center with expected outcomes. This is a critical part of the quality improvement process that must occur at every institution.

KEY POINTS: PROSPECTIVE RISK ASSESSMENT IN PEDIATRIC CARDIAC SURGERY AND CARDIOLOGY

- The RACHS-1 and ABC scores are two validated systems to estimate risk of mortality according to surgical complexity.
- The STAT score is a new risk model developed from empiric outcome data and promises to be the most accurate method for estimating risk preoperatively.
- The CHARM project estimates the risk of adverse outcomes according to complexity of the interventional cardiac catheterization procedure.

Closed claims analysis in anesthesia

The American Society of Anesthesiologists has sponsored multiple investigations using a “closed claims” analysis method to identify areas of concern for anesthesiologists,
### Table 3.1  
Society of Thoracic Surgeons–European Association for Cardio-Thoracic Surgery Congenital Heart Surgery (STAT) Mortality Score Categories

<table>
<thead>
<tr>
<th>Mortality category 1 (0.55%, 0–1%)</th>
<th>Mortality category 2 (1.7%, 1–2.2%)</th>
<th>Mortality category 3 (2.6%, 1.1–4.4%)</th>
<th>Mortality category 4 (8.0%, 6.3–11.1%)</th>
<th>Mortality category 5 (18.4%, 13.9–27.9%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASD repair (patch)</td>
<td>PDA closure, surgical</td>
<td>Transplantation, lungs</td>
<td>Mitral valve replacement</td>
<td>DKS procedure</td>
</tr>
<tr>
<td>AVC repair, partial</td>
<td>PA, reconstruction main trunk</td>
<td>Occclusion MAPCAs</td>
<td>Pericardial drainage procedure</td>
<td>Transplantation, heart-lung</td>
</tr>
<tr>
<td>ASD + PAPVC</td>
<td>LV to aorta tunnel repair</td>
<td>Coarctation + VSD repair</td>
<td>Aortic arch repair</td>
<td>ccTGA, atrial switch, Rastelli</td>
</tr>
<tr>
<td>Aortic stenosis, subvalvular</td>
<td>Valvuloplasty, mitral</td>
<td>Konno procedure</td>
<td>Fontan revision or conversion</td>
<td>ccTGA, atrial switch, ASO</td>
</tr>
<tr>
<td>AICD implantation</td>
<td>Valvuloplasty, aortic</td>
<td>Coarctation, patch aortoplasty</td>
<td>DORV repair</td>
<td>Norwood procedure</td>
</tr>
<tr>
<td>DCRV repair</td>
<td>1 1/2 ventricular repair</td>
<td>PA, reconstruction branch central</td>
<td>DORV, intraventricular tunnel</td>
<td>Truncus + IAA repair</td>
</tr>
<tr>
<td>ASD repair (primary)</td>
<td>Arrhythmia surgery, ventricular</td>
<td>Pulmonary artery aneurysm repair</td>
<td>Arterial switch + aortic arch repair</td>
<td></td>
</tr>
<tr>
<td>VSD repair (patch)</td>
<td>Pacemaker, permanent</td>
<td>Right ventricular aneurysm repair</td>
<td>PA debanding</td>
<td></td>
</tr>
<tr>
<td>Vascular ring repair</td>
<td>Ross procedure</td>
<td>VSD septal fenestration</td>
<td>ASO + VSD repair</td>
<td></td>
</tr>
<tr>
<td>Coarctation repair, end–end</td>
<td>Glenn + PA reconstruction</td>
<td>Shunt, ligation and takedown</td>
<td>Cardiac tumor resection</td>
<td></td>
</tr>
<tr>
<td>AICD procedure</td>
<td>Aortotompy</td>
<td>Hemi-Fontan</td>
<td>Transplantation, heart</td>
<td></td>
</tr>
<tr>
<td>PFO, primary closure</td>
<td>Fontan, atripulmonary</td>
<td>A/V repair, complete</td>
<td>Coronary artery bypass</td>
<td></td>
</tr>
<tr>
<td>AVR, bioprosthetic</td>
<td>Bilateral bidirectional Glenn</td>
<td>Arterial switch operation</td>
<td>TOF – absent PV</td>
<td></td>
</tr>
<tr>
<td>VSD repair (primary)</td>
<td>Aortic root replacement, mechanical</td>
<td>Valvuloplasty, truncal</td>
<td>Valve excision, tricuspid</td>
<td></td>
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<tr>
<td>PVR</td>
<td>Conduit, LV to PA</td>
<td>Fontan, aticroventricular connection</td>
<td>Shunt, systemic to pulmonary</td>
<td></td>
</tr>
<tr>
<td>Conduit reoperation</td>
<td>Coarctation, extended end-end</td>
<td>Pulmonary embolectomy, acute</td>
<td>TOF-AVC repair</td>
<td></td>
</tr>
<tr>
<td>TOF, ventriculotomy, non-transannular</td>
<td>Anomalous origin coronary artery</td>
<td>ASD, partial closure</td>
<td>Ross–Konno</td>
<td></td>
</tr>
<tr>
<td>Glenn, unidirectional</td>
<td>RVOT procedure</td>
<td>Rastelli operation</td>
<td>Senning</td>
<td></td>
</tr>
<tr>
<td>AVC repair, intermediate</td>
<td>Aortic aneurysm repair</td>
<td>Conduit, ventricle to aorta</td>
<td>Ebstein's repair</td>
<td></td>
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<tr>
<td>Coarctation repair, interposition graft</td>
<td>ccTGA, VSD closure</td>
<td>AVR, homograft</td>
<td>Aortic arch + VSD repair</td>
<td></td>
</tr>
<tr>
<td>Fontan, TCPC, lateral tunnel, fenestrated</td>
<td>AP window repair</td>
<td>REV</td>
<td>PA banding</td>
<td></td>
</tr>
<tr>
<td>Sinus of Valsalva repair</td>
<td>Valvuloplasty, pulmonic</td>
<td>Pulmonary artery sling repair</td>
<td>Aortic root replacement, homograft</td>
<td></td>
</tr>
<tr>
<td>AVR, mechanical</td>
<td>TOF, ventriculotomy, transannular</td>
<td>Mustard</td>
<td>Unifocalization, MAPCAs</td>
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<tr>
<td></td>
<td>Aortic root replacement, bioprosthetic</td>
<td>Pulmonary atresia-VSD</td>
<td>Aortic dissection repair</td>
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</tr>
<tr>
<td></td>
<td>Bidirectional Glenn</td>
<td>Conduit, RV to PA</td>
<td>ccTGA, VSD and LV to PA conduit</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aortic stenosis, supravalvular</td>
<td>Pulmonary embolectomy</td>
<td>Pulmonary atresia – VSD – MAPCA</td>
<td></td>
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</tbody>
</table>

(continued overleaf)
Table 3.1  

<table>
<thead>
<tr>
<th>Mortality category 1 (0.55%, 0–1%)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Pericardectomy</td>
<td>Conduit placement, other</td>
<td>LV aneurysm repair</td>
<td>VSD creation, enlargement</td>
<td>Interrupted aortic arch repair</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fontan, TCPC, external fenestrated</td>
<td>HLHS biventricular repair</td>
<td>ASO + VSD + aortic arch repair</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pulmonary origin from ascending aorta</td>
<td>Pulmonary venous stenosis repair</td>
<td>Truncus arteriosus repair</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ASD, common atrium</td>
<td>Shunt, systemic to pulmonary central</td>
<td>ASD creation/enlargement</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PAPVC, scimitar</td>
<td></td>
<td>Atrial septal fenestration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fontan, TCPC, external non-fenestrated</td>
<td></td>
<td>Valve closure, tricuspid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pulmonary artery ligation</td>
<td></td>
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<td>Coronary artery ligation</td>
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<td>Aortic root replacement, valve</td>
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<td>sparing</td>
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<td>Mitral stenosis, supravalvular ring</td>
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<td>Arrhythmia surgery, atrial</td>
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<td>Systemic venous stenosis repair</td>
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<td>PA, reconstruction, branch</td>
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<td>peripheral</td>
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<td>Valvuloplasty, tricuspid</td>
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<td>TVR</td>
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<td>Valve replacement, truncal</td>
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<td>Fontan, TCPC, lateral tunnel</td>
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<td>non-fenestrated</td>
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<td>Atrial fenestration closure</td>
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<td>Cor triatrium repair</td>
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<td>VSD, multiple</td>
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<td>Atrial baffle procedure</td>
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<td>Coarctation, subclavian flap</td>
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<td>Partial LV reduction surgery</td>
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<td>TOF, RV-PA conduit</td>
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*Expected STAT score model-adjusted percent mortality before hospital discharge from surgical procedure, with 95% confidence interval (CI).  
ASD, atrial septal defect; AVC, atrioventricular canal; PAPVC, partial anomalous pulmonary venous connection; AICD, automated internal cardiac defibrillator; DCRV, double-chambered right ventricle; VSD, ventricular septal defect; PFO, patent foramen ovale; AVR, aortic valve replacement; PVR, pulmonary valve replacement; TOF, tetralogy of Fallot; TCPC, total cavopulmonary connection; PDA, patent ductus arteriosus; PA, pulmonary artery; LV, left ventricle; RVOT, right ventricular outflow tract; ccTGA, congenitally corrected transposition of the great arteries; AP, aortopulmonary; TVR, tricuspid valve replacement; RV, right ventricle; MAPCAs, major aortopulmonary collateral arteries; REV, réparation à l’étage ventriculaire (REV procedure); DOILV, double outlet left ventricle; DORV, double outlet right ventricle; ASO, arterial switch operation; HLHS, hypoplastic left heart syndrome; TAPVC, total anomalous pulmonary venous connection; DKS, Damus–Kaye–Stansel; IAA, interrupted aortic arch.  
Source: data are from O’Brien et al. [34].
including claims for death and brain injury, central venous line injuries, nerve injury, and airway injury [38–43]. These reports have not generally examined the effects of age or type of surgery and do not have a denominator that is needed to determine the incidence of injury. Jimenez et al. used the closed claims data to investigate pediatric anesthesia liability and segregated the data by type of surgery [44]. This report found that thoracic and cardiac surgeries accounted for slightly less than 10% of all claims that were settled. This figure probably represents a disproportionately high number because of the relative paucity of thoracic and cardiac surgeries compared with all surgeries performed on pediatric patients. Malpractice data are a very insensitive tool for determining the incidence or causality of complications, as so many different factors apart from medical error determine whether or not a claim is initiated or settled. The denominator of pediatric patients undergoing surgical and diagnostic procedures with anesthesia in the United States is not measurable with any accuracy due to the lack of a central reporting mechanism. Examining the caseload at children’s hospitals is insufficient because many procedures are performed in mixed adult–pediatric general hospitals, ambulatory surgical centers, or physicians’ offices. Furthermore, there are well-known weaknesses to using the closed claims data. These analyses rely upon the presence of a settled malpractice claim to be included and the period examined may span decades during which significant changes in anesthesia, medical, and surgical practice have occurred.

**Pediatric and congenital cardiac anesthesia morbidity and mortality**

Over the last decade, a number of manuscripts concerning cardiac arrest in children have been published, some of which focused on children with CHD, with others focusing on children undergoing all types of surgical and non-surgical procedures [28,29,45,46]. The Pediatric Perioperative Cardiac Arrest (POCA) Registry was a multi-institutional effort in which participants anonymously reported all episodes of cardiac arrest in children aged 18 and younger that resulted in chest compressions or death at the time of surgery or within 24 hours. This project was begun in 1994 and data collection and analysis continued through 2004, at which time further data collection was put on hold. Subsequent examination of the detailed data forms allowed the investigators to assess the relative contribution of anesthesia to the cardiac arrest or death. The most recent publication from the POCA group was a follow-up to their original publication in 2000, and focused the analysis on arrests in patients with heart disease [47,48]. The authors reported that cardiac arrests in these patients were more likely to be in unrepaired patients (59%) or palliated patients (26%) than in patients with repaired cardiac lesions (15%). In 2010, Ramamooorthy et al. re-examined the POCA data, specifically assessing children with congenital heart defects [49]. Overall, they found that of the 373 anesthesia-related cardiac arrests, 127 (34%) patients had congenital or acquired heart disease – a number, not surprisingly, far out of proportion to the incidence of heart disease in the pediatric population (0.8%). Patients with single ventricle physiology were those most likely to suffer a cardiac arrest, while those with aortic stenosis and cardiomyopathy were associated with the highest mortality rates.

Building on the scope of the POCA registry, the Wake Up Safe (WUS) Database is, at the time of writing, a voluntary registry of 19 pediatric hospitals in the US, organized to record serious adverse events during the perioperative period [50]. The aim of this project is not only to collect data on cardiac arrest events like POCA, but also to continuously collect data on adverse events or “near misses,” such as acute lung injury, musculoskeletal injury, spinal cord injury, or surgery on the wrong patient/site. An initiative started by the Society for Pediatric Anesthesia (SPA) in 2009, WUS hopes to provide ongoing monitoring of these very rare events across multiple institutions, and to use these data to uncover ways to prevent them from recurring. Because of the way in which the WUS initiative is structured, it will be possible to determine the incidence of these events and not just record their existence. It is, however, limited at this time to only a relatively small number of major pediatric centers and does not encompass many locations outside of these centers where the majority of pediatric cases occur such as ambulatory surgery centers, private offices (such as dental operatories), and general community hospitals.

Since the WUS project began, statements have been published on their website concerning hyperkalemia, preventing wrong site procedures, and decreasing the risks of intravenous medication errors. A recently published paper reported the first WUS database analysis: of 736,365 pediatric anesthetics of all subspecialties in the database there was a serious adverse event rate of 1.4/1,000 anesthetics, with respiratory events most common (254 of 740) and cardiac arrest the next most frequent (241) [51].

The investigators at Boston Children’s Hospital have been collecting anesthetic data on their own patients since January 2000, both for internal quality and for state reporting requirements in Massachusetts. The publication of this data through December 31, 2005 from their cardiac ORs represents a significant effort to determine contemporary complications specific to pediatric cardiac anesthesia-related morbidity [28]. One of the difficulties associated with determining causality in this patient population is the interdependent nature of anesthesia, surgery, and patient physiology. The authors examined each incident with a panel of three pediatric cardiac anesthesiologists, with a subsequent review by a pediatric cardiac surgeon, before assigning causality. Boston Children’s Hospital reported that in their series of 5,213 cardiac surgical patients from 2000 to 2005, there were 41 cardiac arrests in 40 patients for an overall frequency of 0.79%, with anesthesia playing a significant role in 11 of the 41 cases, or, in other words, 21.1 cardiac arrests per
10,000 anesthetics. This compares with their previously reported anesthesia-related incidence of 2.7 cardiac arrests or death per 10,000 anesthetics in all pediatric patients during roughly the same time period [52]. In 2013, the investigators from Boston Children’s Hospital again reviewed their institutional databases to examine the incidence of cardiac arrest in children with CHD undergoing cardiac catheterization and describe potential risk factors for anesthesia [45]. In total, 7,289 catheterization procedures were performed between January 1, 2004 and December 31, 2009, and were classified as either a biopsy (19%), diagnostic (25%), or interventional catheterization (58%) [45]. Seventy procedures were associated with a cardiac arrest, with a reported frequency of 0.96/100 cardiac catheterizations. The authors acknowledge that although the frequency of arrest is higher than other multi-institutional reports, it is comparable to the results of their prior study on the incidence of arrest in the cardiac OR. The incidence of cardiac arrest in the population studied was found to be statistically significantly higher for children undergoing interventional procedures and those who were younger at the time of the procedure ($P < 0.001$). These authors concluded that these high-risk patients should be managed by an anesthetic team familiar with the pathophysiology, cases, environment, and perioperative staff, in order to facilitate communication and prompt resuscitation should the need arise. There also appeared to be an overall decline in the incidence of cardiac arrest when sedation and anesthesia were provided more routinely by a dedicated pediatric cardiovascular anesthesia team in the latter half of the data collection period.

Another institution with a long history of anesthesia data collection, the Mayo Clinic in Rochester, MN, also reviewed their experience with cardiac arrests in children [29]. A consistent factor in all of these studies is that children with underlying congenital cardiac defects are at a much higher risk of cardiac arrest than children without these defects. The incidence of cardiac arrest at the Mayo Clinic for children during non-cardiac procedures was 2.9/10,000, as compared with 127/10,000 for children undergoing cardiac procedures, a 30-fold increase in risk. Sub-analysis related to causality, age, and type of surgery further stratified their data. Of their 92,881 patients, 4,242 were for cardiac procedures. Within the 54 children who suffered a cardiac arrest or death undergoing a cardiac procedure, age played a significant role, with neonates having the highest risk. Anesthesia was not identified as a causative factor in any of the cardiac surgical arrests or death. At the Royal Children’s Hospital, Melbourne, Australia, van der Griend and colleagues examined anesthesia-related mortality in 101,885 anesthetics administered to 56,263 children from January 1, 2003 through August, 2008 [46]. They, too, utilized an expert review panel of three senior anesthesiologists, examining the record of every patient who died during this time period who had received an anesthetic in the preceding 30 days. Overall anesthesia-related mortality was found to be 1 in 10,188 cases (0.98/10,000). All 10 deaths where anesthesia was found to be a contributing factor had significant pre-existing conditions, with pulmonary hypertension present in 50%. There were no anesthetic-related morbidities in children without underlying medical problems. Overall mortality was significantly higher in children < 30 days old and those with cardiac disease (particularly after 30 days of life).

As is evident from the most recent data, even the busiest of programs only infrequently have anesthesia-related cardiac arrests or death, because of the low incidence of these events. As a consequence, it is necessary to harvest data over many years to collect any meaningful numbers, during which time major changes in patient management may occur. For example, the initial POCA study attributed many arrests to the use of the anesthetic agent halothane, a known cardiac depressant [48]. By the time of the follow-up publication 7 years later, halothane had been replaced almost entirely in North America by sevoflurane, an anesthetic agent with significantly less cardiotoxicity at the typically administered doses.

**KEY POINTS: PEDIATRIC AND CONGENITAL CARDIAC ANESTHESIA MORBIDITY AND MORTALITY**

- The POCA Registry reported that 34% of cardiac arrests under anesthesia had heart disease as a factor.
- The Boston Children’s Hospital registry has reported a cardiac arrest rate of 0.79% for cardiac surgery, and 0.96% for cardiac catheterization.
- The Mayo Clinic study reported a 30-fold increase in risk of cardiac arrest with cardiac surgery vs. non-cardiac surgery in pediatric patients.
- The Royal Children’s Hospital study reported that pulmonary hypertension was a factor in 50% of anesthesia-related deaths.

**CCAS and the Congenital Cardiac Anesthesia Network (CCAN)**

The Congenital Cardiac Anesthesia Society was formed in 2005 by representatives from many of the busiest congenital cardiac surgical programs in North America. It is a subsidiary of the SPA and its work is closely coordinated with that organization. Membership is open to all individuals providing anesthesia-related care for children with heart defects or an interest in the field and it currently has almost 700 members both from the US and internationally. In addition to educational programs at its conferences and as a sponsor of other educational efforts, a major function of the organization is the development of a data registry linked to the STS-CHSD. In the UK and Ireland, CCAN is an informal organization of pediatric cardiac anesthetists numbering 70–80 physicians, which sponsors...
an annual meeting for presentation of timely topics and discussion/debate about clinical practices. CCAN also sponsors a mailing list for regular updates.

**Joint CCAS–STS database initiative**

The Joint CCAS-STS Congenital Cardiac Anesthesia Database is a collaborative project developed over the last decade by multiple parties interested in capturing anesthesia-related information on these high-risk patients. The process by which this project came about is described elsewhere [8]. Anesthesia-related data fields for the database are selected by a database committee of the CCAS in coordination with the existing fields in the STS-CHSD. For an additional fee, STS-CHSD participating centers may elect to submit their anesthetic data to be pooled anonymously with the other participating centers during their annual data harvest. Importantly, the anesthesia data set includes information on congenital cardiac patients undergoing procedures outside of the cardiac ORs, including cardiac catheterization and non-cardiac surgical procedures. As noted previously, these patients represent a particularly high-risk subset of the pediatric population.

The interdependent relationship between congenital cardiac surgery and congenital cardiac anesthesia supports the creation of a common database for these subspecialties. Multiple potential benefits are being realized through the development of this joint database:

- Minimization of data entry burden
- Minimization of costs associated with data entry
- Minimization of the cost associated with database maintenance
- Utilization of common nomenclature based on The International Pediatric and Congenital Cardiac Code [53]
- Utilization of common database fields
- Utilization of common database definitions
- Utilization of common database standards
- Development of common strategies to report outcomes
- Development of common quality improvement initiatives

The Joint CCAS-STS Congenital Cardiac Anesthesia Database began collecting data in January 2010. The data is harvested semi-annually. As of the Fall 2013 harvest, over 41,000 distinct anesthesia records have been analyzed from 35 programs in the US. These anesthesia centers represent a large cross-section both geographically and in terms of volume. Surgical cases represent 66% of the caseload while cardiology cases account for 18%, and “other” cases (thoracic, non-cardiac/non-thoracic procedures on cardiac patients) represent the remaining 16%.

Adverse events were reported overall in 790 of the 40,218 (1.9%) cases. The most common adverse event reported (other than difficulty obtaining vascular access within 1 hour) was unanticipated difficulty with intubation (145 incidents, 0.4%). Cardiac arrest unrelated to surgical or procedural manipulations occurred 76 (0.2%) times. The STS-CHSD, including the anesthesia component, is updated approximately every 3 years. The most recent update became active on January 1, 2014. The CCAS Database Committee has made several modifications to the data being collected, including multiple additions to the adverse outcome reporting options. The committee also worked with the STS to consolidate and clarify duplication of data entry items, such as blood transfusion categories, and added additional medication and blood product categories to reflect newer pharmacologic options. The complete data collection forms are available on the STS website, as is information about how to become a participating center [54]. Table 3.2 lists the adverse events being collected by the CCAS–STS-CHSD.

**International efforts**

Efforts are ongoing to make this database initiative a global project. Initial collaborative discussions have taken place about the possibility of linking this initiative with the European Association of Cardiothoracic Anaesthesiologists [55]. The final selection of database fields will be made through a collaborative effort involving surgeons and cardiologists from Europe and North America, as well as other continents. It is certainly possible and desirable that the STS-CHSD has an identical anesthesia module in the congenital heart database of EACTS and The European Congenital Heart Surgeons Association. These European and North American congenital heart surgery databases have functioned as sister databases with identical nomenclature and database fields and definitions [56,57]. The incorporation of anesthetic data into the effort should follow a similar strategy. This project should also ideally spread beyond North America and Europe. Efforts to involve Africa, Asia, Australia, and South America are necessary and already underway, under the leadership of The World Society for Pediatric and Congenital Heart Surgery [58].

The creation of a joint cardiac surgery and anesthesia database is another step towards the ultimate goal of creating a database for CHD that spans both geographic and subspecialty boundaries and can potentially capture a patient’s lifetime of cardiac care regardless of their location. The Pediatric Heart Network, a research consortium of major congenital cardiac centers, has recognized this need and is supporting the creation of linkage between various registries such as the CCAS, STS, EACTS, Congenital Heart Surgeons’ Society, the ACC IMPACT Interventional Cardiology registry, and the Pediatric Cardiac Critical Care Consortium (PC4) ICU registry, as well as others [59].

Measuring outcomes has become a critical component of all facets of medical practice today. It is important for anesthesia and, in particular, for practitioners of pediatric cardiac anesthesia because of the extremely high-risk nature of this practice. Regular review of both caseload and outcomes in a structured manner through quality improvement conferences, mortality and morbidity, and
<table>
<thead>
<tr>
<th>Event</th>
<th>Definition</th>
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<tr>
<td><strong>None</strong></td>
<td>No anesthesia-related adverse events noted in the perioperative period</td>
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<tr>
<td><strong>Airway – respiratory events</strong></td>
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<tr>
<td>Oral/nasal injury – bleeding</td>
<td>Bleeding noted in oropharynx or epistaxis, dental, lip or nasal injury</td>
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<tr>
<td>Respiratory arrest</td>
<td>Need to intervene in airway management in unplanned way (i.e., converting from cannula to ETT or LMA to ETT)</td>
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<tr>
<td>Laryngospasm requiring medication</td>
<td>Laryngospasm requiring medical intervention other than positive pressure</td>
</tr>
<tr>
<td>Difficult intubation/reintubation</td>
<td>Unplanned difficult intubation or reintubation</td>
</tr>
<tr>
<td>Bronchospasm</td>
<td>Wheezing requiring medical intervention other than suctioning</td>
</tr>
<tr>
<td>Hemoptysis/pulmonary hemorrhage</td>
<td>Bleeding either from endotracheal tube or postoperative hemoptysis</td>
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<tr>
<td>Stridor/subglottic stenosis</td>
<td>New-onset stridor noted after extubation requiring intervention</td>
</tr>
<tr>
<td>Extubation</td>
<td>Unplanned extubation (except if TEE-related – see below)</td>
</tr>
<tr>
<td>Endotracheal tube migration</td>
<td>Endotracheal tube needing to be repositioned in ICU on arrival chest X-ray</td>
</tr>
<tr>
<td>Airway injury</td>
<td>Barotrauma/pneumothorax secondary to positive pressure ventilation</td>
</tr>
<tr>
<td>Pulmonary hypertensive crisis</td>
<td>Probable or definite PH crisis requiring intervention</td>
</tr>
<tr>
<td>Unplanned need to remain intubated due to anesthesia</td>
<td>Need to remain intubated at conclusion of procedure due to anesthesia factors (oversedation, muscle relaxation)</td>
</tr>
<tr>
<td>Hypercyanotic episode (“tet” spell)</td>
<td>Hypercyanotic episode (decrease in SpO₂ &gt; 20% from baseline) requiring intervention other than establishing airway (“Tet” spell)</td>
</tr>
<tr>
<td><strong>Vascular access events</strong></td>
<td></td>
</tr>
<tr>
<td>Arrhythmia – CVL placement</td>
<td>Arrhythmia therapy needed other than withdrawing wire or catheter</td>
</tr>
<tr>
<td>Myocardial injury – CVL placement</td>
<td>Myocardial perforation</td>
</tr>
<tr>
<td>Vascular compromise – CVL placement</td>
<td>Extremity ischemia or compromise with CVL placement</td>
</tr>
<tr>
<td>Pneumothorax – CVL placement</td>
<td>Pneumothorax during placement of CVL</td>
</tr>
<tr>
<td>Vascular access</td>
<td>Inability to obtain desired vascular access within 1 hour of induction anesthesia (PIV/Aline/CVL)</td>
</tr>
<tr>
<td>Hematoma requiring relocation of catheter</td>
<td>Significant hematoma that requires changing site of desired access</td>
</tr>
<tr>
<td>Arterial puncture</td>
<td>Inadvertent arterial puncture during CVL placement</td>
</tr>
<tr>
<td>Intravenous/intra-arterial air embolism</td>
<td>Air embolism causing hemodynamic change or ischemia</td>
</tr>
<tr>
<td>Arterial line placement – extremity ischemia</td>
<td>Extremity ischemia or compromise with arterial line placement</td>
</tr>
<tr>
<td>Intravenous Infiltration</td>
<td>Peripheral or central IV infiltration</td>
</tr>
<tr>
<td><strong>Regional anesthetic events</strong></td>
<td></td>
</tr>
<tr>
<td>Bleeding – regional anesthetic site</td>
<td>Bleeding at site of regional anesthetic placement</td>
</tr>
<tr>
<td>Intrathral puncture – regional</td>
<td>Inadvertent intrathral puncture during caudal or epidural placement</td>
</tr>
<tr>
<td>Local anesthetic toxicity – regional</td>
<td>Systemic evidence of local anesthesia toxicity (ECG changes, CNS changes)</td>
</tr>
<tr>
<td>Neurologic injury – regional</td>
<td>Injury to peripheral nerve during regional nerve block</td>
</tr>
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<td><strong>Drug-related events</strong></td>
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<tr>
<td>Anaphylaxis/anaphylactoid reaction</td>
<td>Suspected anaphylactic/anaphylactoid reaction requiring intervention for either hemodynamic support or respiratory intervention</td>
</tr>
<tr>
<td>Non-allergic drug reaction</td>
<td>Non-anaphylactic reaction such as “red man” syndrome or hypotension</td>
</tr>
<tr>
<td>Medication administration</td>
<td>Wrong medication administered</td>
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<tr>
<td>Medication dosage</td>
<td>Wrong dosage of correct medication</td>
</tr>
<tr>
<td>Intraoperative recall</td>
<td>Recall of intraoperative events</td>
</tr>
<tr>
<td>Malignant hyperthermia</td>
<td>Suspected or confirmed malignant hyperthermia reaction requiring dantrolene</td>
</tr>
<tr>
<td>Protamine reaction</td>
<td>Significant reaction to protamine requiring intervention other than slowing administration</td>
</tr>
<tr>
<td><strong>Cardiac arrest events</strong></td>
<td></td>
</tr>
<tr>
<td>Cardiac arrest – anesthesia-related</td>
<td>Cardiac arrest requiring CPR during anesthesia care not related to surgical or catheter manipulation</td>
</tr>
<tr>
<td>Cardiac arrest – not anesthesia-related</td>
<td>Cardiac arrest requiring CPR during surgical or catheter manipulation</td>
</tr>
<tr>
<td><strong>TEE-related events</strong></td>
<td></td>
</tr>
<tr>
<td>TEE-related esophageal bleeding/injury</td>
<td>TEE-related esophageal bleeding noted during or after TEE removal</td>
</tr>
<tr>
<td>Esophageal chemical burn</td>
<td>TEE-related injury to esophageal mucosa due to TEE cleaning chemicals</td>
</tr>
<tr>
<td>TEE-related airway compromise</td>
<td>TEE-related compromise of ventilation or oxygenation requiring removal of TEE</td>
</tr>
<tr>
<td>TEE-related extubation</td>
<td>TEE-related inadvertent extubation of patient</td>
</tr>
</tbody>
</table>
individual case reviews can help to educate anesthesia departments and individuals and perhaps minimize future adverse outcomes. Open lines of communication with our surgeons, cardiologists, and intensive care physicians are a key component of this process, along with the recognition that adverse events are inevitable in such a system and our job is always to be vigilant and ready to act on the patient’s behalf.

**KEY POINTS: NETWORKS AND DATABASES**

- A major database effort has been initiated by CCAS in conjunction with the STS Congenital Heart Surgery Database.
- Both cardiac surgical and non-cardiac surgical anesthetics can be entered, and as of 2013, 41,000 anesthetics from 35 US programs have been analyzed.

**Selected References**
A full reference list for this chapter is available at:
http://www.wiley.com/go/andropoulos/congenitalheart


34 O’Brien SM, Clarke DR, Jacobs JP, et al. An empirically based tool for analyzing mortality associated with congenital heart surgery. J Thorac Cardiovasc Surg 2009;138:1139–53. The description of the STAT mortality score modeled utilizing over 70,000 records from two databases, and dividing pediatric cardiac surgical procedures into five levels of mortality categories based upon the observed outcomes rather than a priori assignment by expert opinion. This process was then validated by comparison to a larger sample set of over 111,000 pediatric cardiac surgical cases.

catheterization, using data generated from five large cardiac catheterization centers in the US.


CHAPTER 4

Development of the Cardiovascular System and Nomenclature for Congenital Heart Disease*

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Introduction

Congenital heart disease (CHD) is the most common birth defect, occurring in 0.8% of live births and accounting for almost one-third of all major congenital anomalies [1,2]. The etiology and mechanisms of congenital cardiac malformations are not yet fully understood, and much of our understanding is derived from vertebrate animal models and progress in genomics, proteomics, transgenesis, imaging, and integrative systems biology [3]. Although cardiac anomalies are sometimes considered to have genetic and non-genetic causes, the multifactorial inheritance of some lesions is probably due to the interactions between several genes and modulating environmental factors, including known teratogens (such as alcohol, isotretinoin, and anticonvulsants), infectious agents (such as rubella), or maternal disease (such as diabetes mellitus and obesity) [4,5]. Developmental mechanisms include genetic and epigenetic molecular events, signaling, cell migration, and hemodynamic and contractile forces [6]. Analyses of the signaling pathways and regulatory factors that affect cardiac morphogenesis have begun to explain what causes specific cell lineages to commit to certain regions of the heart and how cardiac development is guided by decisions regarding cell migration, differentiation, proliferation, and death [4,7–9]. Furthermore, it has recently been recognized that the genes and developmental mechanisms producing CHD also play a role in the pathogenesis of cardiac dysfunction in adults with CHD [8,10]. Determining the cell lineages in the embryo has provided an insight into adult lineages and has opened the door for using regenerative medicine and novel therapies to treat congenital and acquired heart disease. It must be stated that much of the knowledge and understanding we have regarding cardiovascular development was derived from research in non-human species, which was performed with the hope that the same processes occur in humans. For detailed foundational information on the cell biology of cardiac development, the reader is referred to two excellent textbooks, Cardiac Development by Margaret Kirby [11], which is cited frequently in this chapter, and Heart Development and Regeneration, edited by Nadia Rosenthal and Richard Harvey [3].

This chapter consists of two different but somewhat interrelated parts. The first part of the chapter uses an anatomical approach to describe the development of the heart and vascular system and demonstrates the relationships between abnormal development and specific congenital cardiac anomalies. Although a segmental approach is used to describe embryology, cardiovascular...
Development of the cardiovascular system

New concept of cardiac development

Up until the 1990s, the conventional view of cardiac development was based on the **segmental model**, in which the primordiums of all the future components of the heart were hypothesized to be present in the initial heart tube [12]. Many of the classic concepts have been challenged over the past two decades as advancements have been made in labeling and transgenic fate-mapping techniques. Although the labeling studies performed by Stalsberg, de la Cruz, and Viragh from 1969 onwards suggested that cells were added to the poles of the heart from the surrounding mesoderm [13–15], more recent research conducted by Buckingham, Markwald, and others in the chicken and mouse have confirmed that cells are added to the heart after the initial stage of looping [16–18]. As discussed in detail in the following, it is now thought that the primitive heart tube contains little more than the precursors for the left ventricle and that the precursor cells of the other cardiac components are added to both the venous and arterial poles from a second heart field outside the initial heart tube [12]. Elucidation of the genetic and transcriptional networks regulating cardiac development has provided new insight and has increased our understanding of congenital cardiac malformations.

Cardiovascular development: normal and abnormal

The human embryo has no heart or vascular system during the first 2 weeks of life. Instead, it relies on diffusion from the utero-placental circulation. At the end of the second week, the embryo is a bilaminar disc made up of the epiblast and the hypoblast. In vertebrates, the cardiovascular system is the first organ system to develop and function; this begins during the third week of life when diffusion is no longer adequate to meet the nutritional requirements of the embryo. The embryo develops into a trilaminar disc by the process of gastrulation, thereby establishing all three germ layers – the ectoderm, mesoderm, and endoderm. Gastrulation involves cells in the epiblast migrating through the primitive streak caudal to the primitive node. These cells detach from the epiblast (invagination), and some displace the hypoblast to create the embryonic endoderm, others come to lie between the epiblast and endoderm to form the mesoderm, and the remaining epiblast cells form the ectoderm (Figure 4.1) [19]. The epiblast is, therefore, the source of the ectoderm, mesoderm, and endoderm.

Cardiogenic fields

Cardiac progenitor cells are located in the epiblast, just lateral to the primitive streak. After gastrulation, these cells migrate laterally and cranially to the lateral plate mesoderm. The lateral plate mesoderm becomes split by the pericardial coelom into the somatic (dorsal) and splanchnic (ventral) layers (Figure 4.2). Cells in the somatic layer will form the pericardium, and cells located in the bilateral cardiogenic or heart fields in the splanchnic layer will form the myocardium [20]. The heart fields merge in the midline, cranial to the stomatopharyngeal membrane, to form the cardiac crescent (Figure 4.3A,B). There are at least two distinct lineages of cells within the cardiac crescent: one population is referred to as the “first heart field” (FHF), and the other is referred to as the “second heart field” (SHF) [7]. The SHF is contiguous with and located dorsal and medial to the FHF. The FHF will give rise to...
the linear heart tube, and cells from the SHF will be added at the inflow (venous) and outflow (arterial) poles during cardiac looping. Differentiation of the heart field cells into myocardium is dependent on signals from the adjacent endoderm, and the proliferation and differentiation of SHF cells is delayed relative to that of the FHF cells [21]. As discussed in the following, the embryonic cells that contribute to cardiac development arise not only from the heart field mesoderm but also from cardiac neural crest [22] and the proepicardium [23].

**KEY POINTS: CARDIOGENIC FIELDS**

- Myocardial cells are derived from the bilateral cardiogenic or heart fields in the splanchnic layer of the lateral plate mesoderm.
- The heart fields merge to create a cardiac crescent, giving rise to two lineages of cells referred to as the first and second heart fields.
- Cells that contribute to cardiac development originate from heart field mesoderm, cardiac neural crest, and the proepicardium.

**Formation of the heart tube**

The primitive linear heart tube is formed during the fourth week of development from the FHF cells with the folding of the embryo. Contrary to originally held beliefs, the cardiogenic fields do not fuse cranially to caudally in a zipper-like fashion. Folding of the embryo brings the lateral portions of the cardiac crescent together to form the ventral part of the heart tube [24] (Figure 4.3C–G). The medial portions of the cardiac crescent will form the dorsal part of the heart tube, which is suspended from the foregut by the dorsal mesocardium. The heart tube has two caudolateral inlets (venous pole) and one craniomedial outlet (arterial pole) [24,25]. After folding of the embryo, the SHF mesoderm is located in the dorsal pericardial wall. The schematic drawings in embryology textbooks illustrating the presence of all the cardiac segments in the straight heart tube prior to looping are hypothetical constructions, as most of the segments are added to the primitive heart tube during the looping stages [26].

The myocardium of the heart tube is called primitive or primary because, unlike adult working myocytes, the myocytes of the heart tube have few contractile elements, a poorly developed sarcoplasmic reticulum, a low density of gap junctions, and high automaticity [12]. The endocardium is composed of a specialized endothelial cell type that is also derived from the splanchnic mesoderm and develops simultaneously with the myocardium in the cardiac crescent. A distinct population of mesodermal cells in each heart field undergoes de novo vasculogenesis into two hollow endocardial tubes that join to form a single tube. The endocardium becomes contiguous with the endothelium of the developing vasculature. The cardiac jelly, a thick acellular matrix secreted by the myocardium,
Folding the flat embryo positioning the heart

Heart fields and their surroundings

Forming heart tube dorsal view

3D reconstruction ventral view

3D reconstruction dorsal view

Figure 4.3 Folding of the embryo and formation of the heart tube. (A) The embryo starts as a flat disc containing the three germ layers, the ectoderm (Ecto), mesoderm (Meso), and endoderm (Endo). (A–A''') With ongoing folding of the embryo, the embryonic gut that runs from the stomatopharyngeal membrane (SM) to the cloacal membrane (CM) is formed. The heart (HT) becomes positioned ventrally to the foregut (FG), caudally to the head, andcranially to the umbilical cord and transverse septum (TS). HN, Hensen’s node or primitive node. (B) Division of the heart-forming field into the first heart field (1), which will give rise to the linear heart tube and the second heart field (2), which will remain in continuity with the first heart field during subsequent development and from which cardiomyocytes are added to the developing heart. In reality, the strict borders drawn here are gradual. PM, pharyngeal mesoderm. (C–G) Formation of the heart tube from a flat horseshoe-shaped cardiac crescent to a tube. Folding of the embryo brings the lateral portions of the cardiac crescent (red line) together to form the ventral part of the heart tube, while the medial portions of the cardiac crescent (blue line) will form the dorsal part of the heart tube, which is suspended from the foregut by the dorsal mesocardium (DM). After the DM closes and the suspension from the foregut is lost, cells of the second heart field can only be added to the heart via the arterial and venous poles (AP and VP, respectively). (Source: Source: Sylva et al. [24]. Reproduced with permission of Wiley.)

lies between the myocardium and endocardium. The initial heart tube is therefore a tubular structure with an inner endocardial layer, a middle layer of cardiac jelly, and an outer myocardial layer.

Flow in the heart tube is unidirectional. Cardiac contractions start around day 22, and circulation through the embryo begins around day 26. Because the highest automaticity is found at the venous pole, a slow peristaltic contraction moves the blood from the venous to the arterial pole.

Abnormalities of heart tube formation

Clearly, failure of the heart tube to develop (acardia) leads to fetal demise, and as shown in the zebrafish, failure of the bilateral heart fields to fuse results in cardia bifida (two separate hearts in lateral positions) [27].
KEY POINTS: FORMATION OF THE HEART TUBE

- The primitive heart tube forms during the fourth week of development.
- Contractile activity initiates around day 22 and circulation through the embryo begins around day 26 of development.
- Failure of the heart tube to develop results in fetal demise.

Cardiac looping

Looping is a crucial process in cardiac morphogenesis that brings the tubular configuration of the primitive circulation into the correct conformation for chamber specification, septation, and the creation of systemic and pulmonary pathways [26,28]. The heart is not only the first organ to function, but is also the first to develop a bilateral asymmetric form. Cardiac asymmetry is attained during the process of looping.

At first, the heart tube is straight in the ventral midline with paired venous limbs at its caudal end and a single arterial outlet connected to the aortic sac and pharyngeal arch arteries at its cranial end (Figure 4.4) [29,30]. Looping begins with ventral bending (from dorsal to ventral) and the loss of the dorsal mesocardium, which suspends the heart tube from the foregut (ventral pharynx); these changes transform the straight tube into a curved tube (Figure 4.5). This is followed by rotation around the cranio-caudal axis to the right (dextro- or D-looping), bringing the left side of the tube to a ventral (front) position, which is seen as a C-shaped loop with the convexity to the right in a ventral, two-dimensional view [26]. At this stage, the junction of the inflow and outflow limbs is at the deepest convexity. Externally, the junction corresponds to the bulboventricular groove, and internally it corresponds to the bulboventricular fold [31]. Subsequent looping produces a ventral, two-dimensional, S-shaped loop (Figure 4.6). The heart tube lengthens as cells are added in a continuous stream to the venous (inflow) and arterial (outflow) poles by the addition of myocardium (cardiomyocytes) and endocardium from the SHF in the adjacent pharyngeal mesoderm. The poles are the only entryway for new cells from the SHF [32]. The ventricular bend then shifts caudally from its cranial position above the atria, and the inflow region shifts cranially, thereby resulting in convergence of the inflow and outflow poles. After looping, there is rotation (untwisting) of the outflow tract, which results in a leftward shift of the outflow tract. The complex process of cardiac looping is summarized in schematic form in Figure 4.7.

Abnormalities of cardiac looping

Cardiac looping is associated with breaking of the initial bilateral symmetry of the embryo and establishment of the left–right axis [28,30]. The left–right axis is established during gastrulation by nodal cilia at the anterior border of the primitive streak. The cilia sweep from right to left, resulting in leftward flow of extracellular fluid which concentrates a putative secreted factor on the left side of the embryo. Binding of this factor to its receptors triggers asymmetrical gene at the node [28] and expression of Nodal (a member of the TGFβ family [34], Pitx2c (a member of the homeobox gene transcription factor family) is a key regulator of cardiac left–right patterning that acts downstream of Nodal.

Left–right signaling pathways determine not only the direction of looping and the topology of the future ventricular chambers but also the proper development of the atria, the arterial and venous poles, and the systemic vasculature. Abnormalities in left–right patterning increase the incidence of cardiac malformations in both D- and L-loop hearts; typical examples include mirror imagery, atrial isomerism, discordant connections, and heterotaxy [35]. The left–right signaling cascade is hierarchical in that
abnormalities high in the cascade result in randomization of situs, whereas abnormalities lower down, which are associated with tissue-specific signaling, produce discordant connections [24].

Normal cardiac looping to the right, referred to as dextro-looping or D-looping, positions the right ventricle towards the right side and leaves the heart lying predominantly in the left hemithorax with a leftward apex (levocardia) (Figure 4.9, left panel). Situs solitus refers to normal looping with the liver, stomach, and spleen in their normal positions. Rotation around the craniocaudal axis to the left results in a levo-loop (L-loop) heart (Figure 4.9, right panel), in which the right ventricle is positioned towards the left side of the body and the left ventricle towards the right side. Congenitally corrected transposition of the great arteries (CCTGA) arises when the heart (ventricle) loops to the left but the atria and outflow receive correct left–right signals, resulting in both AV and ventriculoarterial (VA) discordance. Situs inversus refers to an L-loop heart with mirror-image reversal, which means the heart lies predominantly in the right hemithorax with a rightward apex (dextrocardia) and there is mirror-image reversal of the liver, stomach, and spleen. Mesocardia refers to a midline heart with the
apex pointing inferiorly or anteriorly. Mesocardia and dextrocardia can be associated with a normal or abnormal arrangement of cardiac structures. Atrial isomerism refers to a bilaterally symmetrical pattern of the atrial appendages (i.e., bilateral leftness or rightness) and is usually associated with severe complex cardiac malformations [28]. Mixed situs occurs when some organs, or components thereof, have normal situs and others have situs inversus. This usually results in complex heart defects known as heterotaxia or heterotaxy syndromes (discussed later in the chapter).

**KEY POINTS: CARDIAC LOOPING**

- Cardiac looping represents a crucial process in cardiac morphogenesis that determines the shape of the heart.
- The process of cardiac looping is complex, resulting in right–left asymmetry in the embryo.
- Normal cardiac looping is to the right, referred to as dextro- or D-looping; abnormal looping to the left results in levo- or L-looping.
Cardiac septation

Cardiac septation begins after looping of the heart tube. It consists of four contemporaneous processes that occur between 27 and 37 days of development, dividing the heart into four chambers and creating separate systemic and pulmonary circulations [36]. Septation is attributable to the muscular septa in the atrial and ventricular chambers, the AV endocardial cushions, the outflow tract endocardial cushions, and the dorsal mesenchymal protrusion.

Atrial septation

Atrial septation takes place in phases to maintain right-to-left atrial shunting and involves the septum primum, septum secundum, and AV canal (AVC) septum. The primary atrial septum (septum primum) grows as a muscular crescent from the craniodorsal wall of the atrium on the right of the pulmonary pit towards the AV endocardial cushions (Figure 4.10). The leading edge of the septum primum is covered by a mesenchymal cap produced by the epithelial-to-mesenchymal transformation of the endocardium covering the septum [32]. This mesenchymal cap is continuous with the protrusion of the dorsal mesocardium (dorsal mesenchymal protrusion), the dorsal (superior) AV endocardial cushion, and the ventral (inferior) AV endocardial cushion [24]. The communication between the leading edge of the septum primum and the AV cushions is known as the primary atrial foramen (ostium primum), which closes when the septum primum becomes contiguous with the fused superior and inferior AV endocardial cushions. Communication between the left and right atria is maintained by the detachment of the septum primum from the roof of the atrial cavity to produce a secondary atrial foramen (ostium secundum) [37]. The secondary atrial septum (septum secundum) is formed by folding of the dorsal wall between the primary atrial septum and the left leaflet of the sinoatrial valve. The septum secundum does not fuse with the AV cushions but remains open as the foramen ovale. The cranial portion of the septum primum remains as a flap valve, which fuses with the edges of the foramen ovale after birth to form the fossa ovalis [32]. The muscular septum between the inferior rim of the fossa ovalis and the AV valves is called the AVC septum.

Early in development, the venous pole of the heart has two channels (the left and right horns of the sinus venosus), returning blood from the embryo (via the cardinal, vitelline, and umbilical veins) to the sinus venosus and common atrium. During the convergence phase of looping, the common atrium expands to the right and left, forming two lateral pouches that will become the right and left atrial appendages [26,38]. Remodeling results in the sinoatrial junction shifting to the right side of the common atrium. The sinus venosus, including its right horn, and the sinoatrial junction become incorporated into the dorsal (back) wall of the right atrium (Figure 4.11). The sinoatrial junction has left and right cranio-caudally oriented valves (venous valves) that meet cranially to form the septum spurium [38]. As the distal portion of the left superior vena cava regresses, the left horn of the sinus venosus becomes smaller and is incorporated into the developing AV groove to become the coronary sinus. The dorsal (back) wall of the left atrium is also formed by incorporation of the pulmonary vein and its surrounding myocardium [32,38].

Defects in atrial septation

The most common cause of an atrial-level shunt is a secundum atrial septal defect (ASD), which is located within the region of the fossa ovalis. It is usually due to a deficiency of the septum primum but, in rare cases, can be caused by a deficiency of the septum secundum [39].

Failure of the septum primum and septum secundum to fuse completely during infancy results in a patent foramen ovale (PFO). As long as the left atrial pressure exceeds the right atrial pressure and the flap valve is large enough to cover the boundaries of the fossa ovalis, the foramen remains functionally closed (probe patent foramen). An ostium primum defect results from failure of the septum primum to fuse with the endocardial cushions. The defect is outside the confines of the fossa ovalis and extends from the inferior limbus of the fossa ovalis to the crest of the interventricular septum. An ostium primum defect is part of the family of AVC defects, also referred to as AV septal and endocardial cushion defects, and may occur in isolation or in association with other abnormalities of the AV junction.

A sinus venosus defect occurs in the area derived from the embryologic sinus venosus (posterior aspect of the right atrium) and is an interatrial communication in which the right atrium connects to the left atrium through one or
Figure 4.9  Handedness of the cardiac loop. Scanning electron micrographs of embryonic chick hearts, viewed from the front, showing the so-called D-loop (dextral-loop) and L-loop (levo-loop) configurations (“C-shaped” loops; HH-stage 12).

Figure 4.10  Schematic drawing illustrating septation of the atria and primary foramen. (A) Chamber-forming heart with the atrioventricular canal (AVC) and outflow tract (OFT) cushions and ridges. The two arrows going down through the AVC into the ventricle represent blood flow during diastole. The two arrows pointing toward the OFT represent blood flow during systole. Note that the primary foramen (PF) is the crossroad of the blood running from the right atrium (RA) to the right ventricle (RV), and the blood running from the left ventricle (LV) to the OFT. (B–F) Sagittal sections at the level of the dotted line in (A). (B) The ventral and dorsal endocardial cushions (1 and 2, respectively) are growing toward each other. (C) The primary atrial foramen (PAF, ostium primum) is closing due to ingrowing of the primary atrial septum (PS, septum primum), with its mesenchymal cap (MC), the dorsal mesenchymal protrusion (DMP), and the endocardial cushions. (C,D) In the PS, small holes appear and merge to form the secondary foramen (SF, ostium secundum). (D–F) The secondary septum (SS, septum secundum) grows to the right side of the PS covering the SF and the rest of the PS, and leaving at the right surface of the atrial septum only the oval fossa (OF) uncovered. A, atrium; LA, left atrium; V, ventricle; 3 and 4, septal and parietal outflow tract ridges, respectively. (Source: Sylva et al. [24]. Reproduced with permission of Wiley.)
more of the pulmonary veins. The most common location for this defect is between the right upper pulmonary vein and the cardiac end of the superior vena cava (SVC type), although in rare cases the right lower/and or middle pulmonary veins and more caudal atrial wall are involved (inferior vena cava [IVC] type) [39].

A coronary sinus defect occurs when the tissue between the coronary sinus and the left atrium is either partially or completely absent (unroofed), resulting in communication between the right and left atria via the coronary sinus orifice. The left-to-right shunt causes enlargement of the coronary sinus orifice.
A common atrium is caused by the absence of the septum primum, septum secundum, and atrial portion of the AVC septum and is usually associated with heterotaxy syndrome [39].

Ventricular septation

After looping of the heart tube occurs, differentiation and re-initiation of cell division by the primary myocardium of the outer curvature causes the ventricles to expand caudally in a pouch-like fashion on either side of the bulboventricular groove (Figure 4.12). De Boer and colleagues [40] have shown that growth of the trabeculae occurs by cellular proliferation at the bases, causing the ventricles to expand or “balloon outwards” (ballooning model of chamber formation). Disappearance of the cardiac jelly results in the formation of trabeculations on the luminal side, producing a spongy-type myocardium. Compact myocardium forms later when epicardially derived fibroblasts infiltrate the epicardial side, at which time proliferation in the trabeculations ceases.

The muscular portion of the interventricular septum is formed by apposition and merging of the medial walls of the expanding ventricles, with cells added mainly from the adjacent left ventricular free wall [24,36]. It is initially crescent-shaped, extending from the inferior (ventral) AVC cushion posteriorly to the superior (dorsal) AVC cushion anteriorly. The space between the free rim of the muscular septum and the fused AV cushions is the primary interventricular foramen. Although the primary interventricular foramen allows for communication between the primitive left and right ventricles, initially, blood from the primitive atrium can only reach the primitive right ventricle via the interventricular foramen. It is only after the AV junction develops that the right atrium will communicate directly with the right ventricle. Closure of the interventricular foramen occurs by fusion of three structures: the superior and inferior endocardial cushions, the muscular interventricular septum, and the endocardial cushions of the outflow tract (conal cushions). The site where these three structures fuse constitutes the membranous part of the ventricular septum. Ventricular septation is usually completed between days 38 and 45 of gestation [41].

Defects in ventricular septation

Ventricular septal defects (VSDs) may be found in isolation or may co-exist with other congenital cardiovascular anomalies. Because the ventricular septum is composed of three components (muscular, AVC endocardial cushion, and outflow tract [conal] cushion), defects at the ventricular level may result from a deficiency of one or more of these structures and/or from their malalignment.

The most common VSDs are those that occur in the muscular portion of the interventricular septum. This type of VSD is surrounded by a rim made completely of muscle. They are often multiple and may be located anywhere in the muscular septum (apical, anterior, mid, or posterior).

The membranous septum is a small, translucent structure. It is adjacent to the anterosetal commissure of the tricuspid valve when viewed from the right side, and it is below the non-coronary leaflet of the aortic valve when viewed from the left. Small defects may spontaneously close after birth due to the presence of the surrounding fibrous tissue (also referred to as aneurysmal tissue). Defects that extend beyond the boundaries of the membranous septum are called para- or perimembranous defects. Membranous VSDs are closely associated with the bundle of His, increasing the risk of causing conduction disturbances during repair.

A conoventricular or subaortic defect is situated between the conal and muscular portions of the ventricular septum and is also close to the bundle of His [41]. These defects are often related to malalignment of the muscular and conal portions of the ventricular septum.

A subpulmonary, conal, supracristal, or doubly committed subarterial defect is located in the outflow tract (conal septum) just below the pulmonary valve. Fibrous continuity between the aortic and pulmonary valves is frequently present. The aortic valve (right cusp or non-coronary cusp) may prolapse into the defect, which may result in aortic regurgitation.

A defect that opens to the inlet portion of the right ventricle may be perimembranous, muscular, or AV [42]. The origin of the AV node and the course of the AV bundle (His) differ for these types, increasing the risk of injury during surgical repair.

A common or single ventricle, defined as the presence of two AV valves with one ventricular chamber or a large dominant ventricle with a diminutive or hypoplastic opposing ventricle may result from various different mechanisms. The pathology may be due to the arrest of or a defect in interventricular septation or from poor alignment of the common AV valve with the ventricles [43]. A wide spectrum of functional single ventricles is recognized. These include double-inlet single ventricle (usually left), defects resulting from atresia or absence of either the right or left AV valve, such as tricuspid atresia, mitral atresia (part of hypoplastic left heart syndrome [HLHS]), those with an atretic semilunar valve (HLHS, pulmonary atresia with intact ventricular septum), unbalanced common AVC defects, and some forms of double-outlet right ventricle.

AV canal septation and AV valve development

The cardiac jelly at the AV junction (and proximal outflow tract) forms into mounds by the myocardial synthesis of extracellular matrix. The endocardial cushions arise from the cells of the endocardium overlying these swellings that invade the cardiac jelly and undergo endocardial-to-mesenchymal transformation into fibroblast-like mesenchymal cells [44]. Prior to valve formation, the endocardial cushions and underlying myocardium prevent the backflow of blood. An inferior endocardial cushion is associated with the outer curvature of the looped heart, and a superior cushion is associated with the inner curvature (Figure 4.10) [29]. Central fusion of the inferior and superior cushions forms the AV septum,
Figure 4.12 Formation of the cardiac chambers. (A–D) Developmental series of mouse embryos. Whole-mount RNA in situ hybridization for the embryonic chamber marker atrial natriuretic factor (ANF) is used as a marker for differentiation into chamber myocardium. (E–G) and (I–L) Schematic drawings of these chamber-forming hearts. Gray, primary myocardium; blue, chamber-forming myocardium; arrows in K indicate the expansion of the chambers eventually leading to the adult configuration, with the ventricles positioned ventro-caudally to the atria. (H) Electron micrograph of a CS14 human heart, demonstrating the similarity with the mouse E11.5 heart and the schematic shown in (L). For didactic purposes, in the schematic in (L), the outflow tract is hinged toward the right side, in vivo it is positioned ventrally to the heart, as depicted in (D) and (H). (A, E, I) The heart tube (HT) consists solely of primary myocardium from the venous (VP) to the arterial pole (AP). (B, F, J) The first chamber to start ballooning is the embryonic ventricle (V) at the outer curvature of the heart. (C, G, K) The heart tube has started to loop and acquire an S shape. An embryonic left and right ventricle are now visible. The atria (A) also start to balloon towards the left and right side. The myocardium of the outflow tract (OFT), inner curvature (IC), and atrioventricular canal (AVC) remains as the primary myocardium. RA, right atrium; LV, left ventricle; CS, equivalent Carnegie stage noted in the left margin of figures. (Source: Sylva et al. [24]. Reproduced with permission of Wiley.)
extends from the level of the valve annuli to fuse with the primary atrial septum, whereas the ventricular portion of the AV septum extends from the level of the valve annuli to form the inlet portion of the interventricular septum. The AVC expands to the right, as does the right ventricle, to allow for direct communication between the presumptive right atrium and the presumptive right ventricle. Smaller cushions develop on the lateral walls (left and right) of the AVC.

The septal leaflet of the tricuspid valve and the anterior leaflet of the mitral valve are derived from the fused inferior and superior endocardial cushions, whereas the mural leaflets are derived from the lateral cushions [45]. Mature AV valves and the subvalvular apparatus are formed by cavitition and remodeling of the cushions and excavation of the underlying ventricular myocardium to form leaflets and chordae tendinea (Figure 4.13) [45,46]. Late in development, the primitive leaflets undergo lengthening and delamination with the disappearance of the myocardial layer.

After the endocardial cushions have fused, the fibroblast-like cells of the cushions are replaced by myocardial cells in a process called myocardialization. Fusion of the nonmyocardial mesenchymal cushions and myocardializatation create part of the atrial septum, ventricular septum, and conal septum, as well as the substrate for the crux of the heart [47].

**Defects of the AVC**

The endocardial cushions of the AVC contribute to the formation of the atrial septum, the ventricular septum, and the mitral and tricuspid valves. The structures derived from the endocardial cushions can have varying degrees of abnormalities, producing a spectrum of lesions called endocardial cushion defects (as previously noted, they are also referred to as AVC or AV septal defects).

At the mildest end of the spectrum is an isolated **cleft in the anterior leaflet of the mitral valve**. An ostium primum ASD is the result of improper fusion of the superior endocardial cushion with the septum primum; although there are two distinct annuli, there is frequently a mitral valve cleft. An **inlet or AVC-type VSD** occurs when the inferior endocardial cushion does not fuse with the muscular component of the ventricular septum. A **transitional AVC defect** is typically an ostium primum defect with a very small to moderate (restrictive) inlet VSD, which is often occluded by AV valve tissue. A **complete AVC (CAVC) defect** comprises an ostium primum ASD, an inlet VSD, and a common AV valve (i.e., the valve leaflets are shared between the left and right ventricles, otherwise referred to as bridging leaflets) in which the leaflets are not adherent to the crest of the ventricular septum. With a CAVC defect, there is reduced wedging of the aortic valve and displacement of the common hinge plane of the AV valve towards the apex so that the apex-to-outlet ventricular dimension is increased and the inlet-to-apex distance is decreased, resulting in a “gooseneck” deformity of the left ventricular outflow tract [48]. In an **unbalanced CAVC defect**, usually one ventricle is hypoplastic and the other receives most of the AV valve tissue because of straddling (insertion of chordae in the opposite ventricle) or override (insertion of chordae to the crest of the septum or the appropriate ventricle). AVC defects may be isolated or may appear as one element of a more complex lesion or syndrome. Approximately 40% of patients with trisomy 21 (Down syndrome) have AVC defects [46].

**Ebstein anomaly** is the most important cause of congenital tricuspid regurgitation and is thought to be due to abnormal delamination of the inlet zone of the right ventricle [49]. The septal and posterior leaflets do not attach to the annulus but are displaced downward toward the right ventricular apex. The portion of the right ventricle that extends from the true tricuspid annulus to the level where the septal and posterior leaflets attach is thin due to partial absence of myocardium and is termed the “atrialized” portion, whereas the trabecular and outlet portions make up the functional right ventricle. The anterior leaflet is large (“sail-like”) and dysplastic and can obstruct the right ventricular outflow tract. Ebstein anomaly can be associated with abnormalities in left ventricular morphology, such as ventricular non-compaction and increased fibrosis of the wall and septum. Most patients with this anomaly have a PFO, and approximately 50% have an ASD [50]. Downward displacement of the leaflets is associated with discontinuity of the central fibrous body, thus producing a substrate for accessory AV connections and ventricular pre-excitation [49].

**Tricuspid atresia** is characterized by agenesis of the tricuspid valve and right ventricular hypoplasia. The region normally occupied by the tricuspid valve may be replaced by an atretic membrane, muscular tissue, or fibrofatty tissue, in which case an ASD would be necessary for survival. With normally related great arteries, blood passes to the lungs through a VSD into a small right ventricle and pulmonary artery, whereas with transposition of the great arteries, blood reaches the lungs directly from the left ventricle. Isolated **tricuspid stenosis** is exceedingly rare.

**Mitral valve stenosis** is most commonly associated with other left-sided obstructive lesions, HLHS being at the most severe end of the spectrum and coarctation of the aorta, aortic arch hypoplasia, and subvalvular or valvular aortic stenosis in Shone’s complex occurring with varying severity. **Congenital mitral regurgitation** is more common than mitral stenosis and is usually associated with AVC defects.

**Outflow tract septation and development of the semilunar valves**

Cardiac neural crest cells are a subpopulation of the cranial neural crest and are crucial for normal cardiovascular development [22]. Cardiac neural crest cells contribute to the formation and remodeling of the aortic arch arteries, outflow tract septation, semilunar valvulogenesis, the
Figure 4.13 Development of the atrioventricular (AV) and outflow tract (OFT) valves and their contributing tissues. (A–H) Sections through mouse hearts in a plane comparable to the schematic heart in panel (S). (B, D, F, H) The lineage contributions of the epicardium is displayed at different developmental stages. The epicardial lineage marker WT1 was used; epicardial lineage is depicted in red, myocardium in green. (I–P) Schematic drawings of valve development in both the atrioventricular canal and outflow tract. Red, epicardium (Ep); gray, primary myocardium; and yellow, endocardial cushion tissue (EC). Note that in the outflow tract the cells are primarily neural crest-derived and not endocardial-derived as in the AV canal. (P) The contribution of the different cushions and ridges to the eventual valves (panel T) is depicted. (Q, R) Display the proepicardium (PE) in a 3-day-old chick embryo. (R) The PE is attached to the heart tube (HT) and spreading out to form the epicardium. Ao, aorta; DAVC, dorsal AV cushion; IR, intercalated ridge; LA, left atrium; LC, lateral cushion; LV, left ventricle; MC, mesenchymal cap; PR, parietal ridge; PT, pulmonary trunk; RA, right atrium; RV, right ventricle; S, septum; SR, septal ridge; VAVC, ventral AV cushion. Equivalent Carnegie stage (CS) is noted in the left margin of figures. (Source: Sylva et al. [24]. Reproduced with permission of Wiley.)
development of cardiac neuronal tissue, and the insulation of the cardiac conduction system [51].

The outflow tract connects the primitive ventricle to the aortic arch arteries and is traditionally divided into three sections: the conus (proximal), the truncus (middle), and the aortic sac (distal) [52]. Septation of the outflow tract begins with the formation of a shelf of mesenchyme in the dorsal wall of the aortic sac in the area between the fourth and sixth pairs of aortic arch arteries [53]. This shelf, called the aorticopulmonary septum, elongates towards the truncus, thereby dividing the lumen of the aortic sac into the future intrapericardial portions of the aorta and pulmonary trunk. Cardiac neural crest cells migrate into pharyngeal arches 3, 4 and 6, and a subset of these cells migrates into the outflow tract (Figure 4.14). The outflow endocardial cushions are ridges of mesenchyme, formed by endocardial-to-mesenchymal transformation of the underlying endocardium, that spiral into the outflow tract. Mesenchymal cells from the pharynx, followed by neural crest cells, invade the truncal cushions to form two centrally placed columns, or prongs, in the shape of an upside-down “U” (Figure 4.15) [54]. These prongs will fuse with the aorticopulmonary septum distally and with the conal cushions proximally. Rotation of the developing pulmonary valve (see later) is associated with spiraling of the aorticopulmonary septum and prongs, so that the developing aorta will connect with the rightward and cranial component of the aortic sac and the developing pulmonary trunk will connect with the leftward and caudal component of the aortic sac [56].

The convergence of the inflow and outflow poles during looping combined with the rotation and wedging processes brings the atria and outflow vessels into concordance with the AV valves and ventricles [52,54]. In the conus, myocardial cells invade the cushions (myocardialization), which then bulge further into the lumen and subsequently meet and fuse in the midline. These conal cushions fuse most proximally with the AV cushion tissue and the crest of the muscular ventricular septum. Muscularization of the central conal cushion tissue and development of the adjacent aortic and pulmonary sinuses produces the subpulmonary infundibulum and a plane of space between the infundibulum and aortic root [56].

The developing pulmonary valve is initially posterior to and left of the developing aortic valve. Morphogenetic movement of the pulmonary valve (posterior to anterior, left of the aortic valve) brings it to its final position anterior and lateral to the aortic valve (Figure 4.8) [57]. This movement of the pulmonary valve is thought to be caused by the development of the subpulmonary conus (infundibulum), which also causes the pulmonary valve to be in a superior position relative to the aortic valve.
Early in development, both the subpulmonary conus and the subaortic conus are situated above the right ventricle. Following torsion and a leftward shift of the outflow tract, resorption and shortening of the subaortic conus causes the aortic valve to sink inferiorly and posteriorly so that it comes to lie directly over the left ventricle and in fibrous continuity with the mitral valve (Figure 4.8) [58]. The conversion from the primitive, single in-series circulation to the double in-series circulation takes place during the fifth week of development.

Following outflow tract septation, the semilunar valves are formed as the mesenchyme in the outflow cushions is remodeled into the trileaflet aortic and pulmonary valves. Initially, three pairs of ridges, consisting of mesenchymal tissue covered by endocardium, protrude into the lumen on each side of the divided truncus [54]. Valve sinuses are formed by excavation on the arterial (distal) face of the cusps. Thereafter, the leaflets are remodeled by mesenchymal apoptosis, blood flow, and shear stress to produce the delicate fibrous tissue seen in mature valves. Cells from the endocardium are the primary source of semilunar and AV valve fibroblasts, but fibroblasts derived from the epicardium also contribute to valve formation [53]. Although neural crest cells are found in the tips of the leaflets, their contribution to valve formation is not fully understood.

Abnormalities of outflow tract septation
The loss or dysfunction of cardiac neural crest cells produces a wide spectrum of conotruncal abnormalities that are associated with syndromes linking defects in the heart, face, and brain [52,54]. These include the 22q11 deletion syndromes, such as DiGeorge and velocardiofacial syndromes, CHARGE syndrome, fetal alcohol syndrome, retinoic acid embryopathy, Alagille syndrome, and Noonan and LEOPARD syndromes [52]. The association between thymus, thyroid, and parathyroid abnormalities in these syndromes is explained by the fact that the neural crest cells contribute to the connective tissue of these three organs. Additionally, abnormalities of the SHF also produce outflow tract defects [54].

Persistent truncus arteriosus results from a failure in outflow tract septation (conotruncus and aorticopulmonary septum) combined with a virtual absence of the subpulmonary infundibulum and, thus, a VSD [59,60]. Typically, the aortic and pulmonary valves are fused to form a single semilunar truncal valve. The origin of the pulmonary arteries from the truncal root varies and is dependent on the degree of the septation deficiency. Incomplete outflow tract septation results in an aortopulmonary window. Aortoventricular tunnels are thought to result from abnormal excavation and maturation of the outflow cushions during the formation of the semilunar valves [56]. Unequal septation can result in either the aorta or pulmonary artery being hypoplastic relative to the other.

Tetralogy of Fallot is thought to result from underdevelopment of the subpulmonary infundibulum (conus) [61]. The smaller infundibulum causes anterior deviation of the conal septum and malalignment of the conal septum with the muscular ventricular septum, producing right ventricular outflow tract obstruction and a subaortic VSD [62]. The pulmonary valve is usually abnormal, and the reduced blood flow contributes, to some degree, to pulmonary artery hypoplasia. Some patients have tetralogy of Fallot with pulmonary valve atresia and varying degrees of hypoplasia of the main and branch pulmonary arteries.

Theories that have been proposed to explain transposition of the great arteries (TGA) include resorption of the subpulmonary conus, causing the pulmonary valve to move inferiorly and posteriorly so that it comes to lie above the left ventricle and in fibrous continuity with the mitral and tricuspid valves [57], and failure of the aortopulmonary septum to spiral [63]. Dextro- or D-TGA refers to TGA with normal looping of the heart to the right, whereas L-TGA refers to looping of the heart to the left [64]. In D-TGA, there is AV concordance and VA discordance. Congenitally or physiologically corrected TGA is characterized by TGA and AV discordance (i.e., double discordance). In the more frequent form, referred to as L-transposition, there is levocardia with situs solitus of the atria and L-looping of the heart. The other form is a mirror image of the above with dextrocardia, inversion of the atria (situs inversus), and D-looping of the heart [65].

Persistence of both the subpulmonary and subaortic coni results in double outlet right ventricle, whereas a deficiency of both results in a double outlet left ventricle (very rare); in either case, there is almost always a VSD.

Fused or absent pulmonary commissures produce pulmonary valve stenosis, in which the valve is typically mobile and dome-shaped with a small and sometimes eccentric orifice [66]. Critical pulmonary valve stenosis is a severe form of pulmonary stenosis that is considered a ductal-dependent lesion because a patent ductus arteriosus (PDA) is essential for pulmonary blood flow.

Obstruction of the left ventricular outflow tract may occur at the valvular, subvalvular, or supravalvular levels. The most common aortic valve anomaly is a bicuspid aortic valve [2]. This malformation is also thought to be the cause of tetralogy of Fallot with pulmonary valve atresia and varying degrees of hypoplasia of the main and branch pulmonary arteries.

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Obstruction of the left ventricular outflow tract may occur at the valvular, subvalvular, or supravalvular levels. The most common aortic valve anomaly is a bicuspid aortic valve [2]. This malformation is also thought to be the most common cardiac defect (occurring in 1–2% of the population). It may be an incidental finding or may result in a clinical presentation in childhood or adult life, and it can occur in isolation or in association with left-sided obstructive lesions [67]. There are several variants, the most frequent being characterized by commissural fusion (most commonly between the coronary cusps), creating a functionally bicuspid structure, and the far less frequent “true” bicuspid valve. Critical aortic valve stenosis in the neonate is a ductal-dependent lesion, in that a PDA is necessary for systemic perfusion. The valve is usually unicommissural or bicommissural and incompletely differentiated with thickened, redundant, and rolled cusps and leaflets consisting of immature loose connective tissue (myxomatous) [68]. Dysplastic valves, rather than commissural fusion, obstruct the orifice. Severe aortic stenosis or aortic atresia can be part of a spectrum of left-sided obstructive lesions associated with hypoplasia of the left ventricle, ascending aorta and/or arch, mitral...
valve stenosis or atresia, and endocardial fibroelastosis of the left ventricle (i.e., HLHS) [69].

Subaortic aortic stenosis has a number of embryologic etiologies. Malalignment of the conal septum with the muscular interventricular septum results in posterior projection of the conal septum into the left ventricular outflow tract and an associated VSD. This pathology may be seen within the context of an interrupted aortic arch.

Familial hypertrophic cardiomyopathy is an autosomal dominant developmental abnormality most commonly due to mutations in the contractile protein (sarcomere) genes, but it may also be due to mutations in non-sarcomeric genes that are associated with mitochondrial defects, potassium channel abnormalities, and abnormalities of protein kinase A [70]. A discrete fibromuscular ridge or membrane below the aortic valve can also cause subaortic stenosis.

Congenital supravalvular aortic stenosis (SVAS) is caused by the deletion of or a loss-of-function mutation in the elastin gene on chromosome 7q11.23. In the majority of cases, SVAS occurs in association with Williams–Beuren syndrome, which is frequently referred to as Williams syndrome (WS) [71,72]. In other cases, SVAS is inherited as an autosomal dominant disorder or results from sporadic mutations and occurs without the mental retardation, elfin facies, distinctive behavioral traits, and neonatal hypocalcemia associated with WS [73]. During the early stages of development, the smooth muscle cells from patients with WS and non-syndromic SVAS express only about 15% and 50%, respectively, of the normal levels of the elastin-precursor tropoelastin [74]. The resultant arterial media has a reduced elastin content, pathologic alignment of the elastin fibers, an increased collagen content, and an increased number of hypertrophied smooth muscle cells. The entire ascending aorta may be narrowed (aortopathy) in about 30% of patients, and up to 80% of patients will have peripheral pulmonary artery stenosis [75].

KEY POINTS: CARDIAC SEPTATION

- Cardiac septation begins after the looping stage with eventual creation of four chambers and two distinct circulations.
- The process of cardiac septation involves the muscular septa in the atrial and ventricular chambers, the AV and outflow tract endocardial cushions, and the dorsal mesenchymal protrusion.
- Abnormalities in this process can result in septation defects at the atrial and/or ventricular levels, altered AV valve development, abnormalities of outflow tract septation, and semilunar valve pathology.

Epicardium and coronary artery development

After looping of the linear heart tube occurs, the epicardium covers the heart as well as the intrapericardial portion and roots of the great arteries. The epicardium is derived from two sources of extracardiac cells: the proepicardial organ (PEO) and the splanchnic mesoderm of the ventral pharynx (Figure 4.15) [23,76]. The venous PEO (vPEO) is derived from mesenchyme near or in the liver and begins as protrusions of splanchnic mesoderm at the venous pole at the back of the pericardial cavity. The vPEO gives rise to the epicardium that will cover the atria, AVC, and ventricles. Likewise, the splanchnic mesoderm of the ventral pharynx at the arterial pole, which is analogous to the PEO at the venous pole or vPEO, gives rise to the epicardium that will cover the outflow tract (arterial PEO or aPEO). Gittenberger-de Groot has shown that after the epicardium has invested the myocardium, a subset of cells undergoes endocardial-to-mesenchymal transformation and migrates into the subepicardial space [77]. These epidermally derived cells (EPDCs) invade the myocardium and endocardial cushions and undergo differentiation into fibroblasts, coronary smooth muscle cells, and endothelial and hematopoietic cells. The epidermally derived fibroblasts become the interstitial fibroblasts, the annulus fibrosus, and the adventitial coronary fibroblasts. The epicardium is necessary for myocardial growth, and interstitial fibroblasts are crucial to the formation of the thick compact myocardium.

Nutrient delivery to the myocardium occurs in three sequential and overlapping phases [47]. Although the early myocardium is avascular, the inner trabecular zone of the myocardial wall has venous sinusoids (trabecular channels) lined by endocardium through which nutrients diffuse. With the formation of the epicardium after cardiac looping, a subepicardial endothelial plexus forms from the EPDCs and undergoes vasculogenesis, angiogenesis, and arteriogenesis [78]. Arteriogenesis is the coating of the initial coronary plexus by smooth muscle cells and pericytes. The coronary plexus penetrates the myocardium, and some of the channels will communicate with the intratrabecular venous sinusoids. The density of the coronary plexus is not uniform across the myocardial wall, being higher on the outer epicardial side than on the inner endocardial side [76]. The subepicardial vascular network later undergoes remodeling to produce the coronary arteries and veins with adult branching characteristics. As reported by Gittenberger-de Groot et al. [78] and Waldo et al. [79], the final step in the development of the coronary circulation is ingrowth of the peritruncal coronary capillary plexus into the base of the aorta (Figure 4.16). Each coronary sinus has an ostium, which receives multiple small vessels. In the right and left aortic sinuses, the multiple channels coalesce to form the main stems of the right and left coronary arteries, whereas the channels in the remaining (non-coronary) sinus regress.

Abnormalities of epicardial development

Normal development of the compact myocardium requires a trophic interaction between the cardiomyocytes and EPDCs [23,80]. Abnormal EPDC function results in ventricular non-compaction, a cardiomyopathy that is characterized by a spongy myocardium and has a predilection for the left ventricle.

Coronary artery fistulae may arise from either the right or left coronary artery and most frequently terminate in the
right heart [81]. Fistulae can occur in isolation or in association with other lesions. In some cases of pulmonary atresia with intact ventricular septum (PA/IVS) and in some forms of HLHS [82], a significant portion of the ventricle may be dependent on blood supply from the hypertensive right (PA/IVS) or left ventricle, respectively. Flow into a lower pressure chamber produces myocardial ischemia by coronary steal and ventricular volume overload.

Vascular channels from the peritruncal ring normally penetrate the aortic sinuses [78]. However, penetration of the pulmonary artery results in an anomalous origin of the coronary artery from the pulmonary artery, the most common form being the left coronary artery arising from the pulmonary artery (ALCAPA) [83,84]. Coronary steal can occur, in which the blood flow is reversed into the pulmonary artery due to the lower vascular resistance of the pulmonary artery and/or the higher pressure of a collateral circulation from the normal coronary artery. Also, blood flowing antegrade through the anomalous coronary artery has a lower oxygen content than normal.

Congenital atresia of the left coronary artery and anomalous aortic origin of the left or right coronary artery from the right or left coronary sinus, respectively, are generally rare but have been associated with sudden death [83,84].

**Development of the conduction system**

The myocardium of the primitive heart tube has no morphologically distinct conducting cells [85,86]. The primitive pacemaker (i.e., area with the cells with the fastest intrinsic rate) is located at the junction of the sinus venosus and the primitive atrium. Before the AV and semilunar valves develop, a unidirectional, slowly transmitted, depolarizing impulse (represented by a sinusoidal electrocardiogram) generates a peristaltic contraction wave that pushes blood from the venous pole to the arterial pole. With elongation of the heart tube, the myocardial cells of the developing ventricular and atrial chambers differentiate into a working myocardial phenotype characterized by fast-conducting gap junctions and sarcomere components [87]. Myocardial cells at the venous pole, AV, and outflow tract differentiate into specialized conductive myocardium. Although these cells have elements of working myocardium (including contraction, autorhythmicity, intercellular conduction, and electromechanical coupling), they retain their primary phenotype of sparse gap junctions and slow conduction (Figure 4.17) [87]. With differentiation of myocytes into working and conductive myocardium, the electrocardiogram resembles that of the formed heart [88].

The *sinus atrial node* (SAN) is detectable at approximately 32 days of gestation. It develops from myocardial cells located at the junction of the right common cardinal vein (which drains into the right horn of the sinus venosus) and the right atrium, ultimately becoming “comma-shaped” with its head at the junction of the SVC and the right atrium and its tail incorporated into the crista terminalis [89]. Nodal cells in the left cardinal vein regress to become the ligament of Marshall [85]. It has now been established that specific conduction pathways through the atrial myocardium do not exist [86,90]. The AV node (AVN) is detectable at approximately 33 days of gestation. It develops from slow-conducting myocardium within the dorsal AV. The AVN becomes located in the triangle of Koch, and the cells of the AVN are in direct continuity with the atrial and ventricular myocardium. The AVN retains its primary phenotype of slow conduction so that there is appropriate AV delay. The AV bundle, left and right bundle branches, and Purkinje fibers develop from fast-conducting ventricular myocardium; the AV bundle from cells in the crest of the interventricular septum, and the bundle branches and Purkinje network from subendocardial myocytes along the ventricular septum [87].

An important step in the development of the conduction system is establishing electrical discontinuity between the atrial and ventricular myocardium at the AV junction. Epicardial cell-derived fibroblasts in the AV groove invade the AV myocardium inferior to the AVN and make contact with the endocardial cushion mesenchyme to form the *annulus fibrosus*, or crux of the heart. Because the annulus fibrosus insulates the atria from the ventricles, the AV conduction system provides the only myocardial continuity between the atria and ventricles.
Abnormalities of conduction system development
Normal development of the conduction system is dependent upon concordance of the atrial and ventricular chambers, correct alignment of the atrial and ventricular septa, and complete closure of the ventricular septum [91]. Thus, from an embryologic perspective, abnormalities of the conduction system would be expected in lesions that involve AV concordance, the AVC, single ventricles, or combinations thereof.

Corrected TGA with L-loop ventricles is associated with displacement of the AVN to an anterior and lateral position within the right atrium; additionally, function of the AV conduction system is suboptimal and can result in spontaneous heart block [91]. In CCTGA with D-loop ventricles and atrial situs inversus, the AVN is typically in a left-sided triangle of Koch. In AVC defects, the AVN is displaced posteriorly to lie low in the atrial septum and anterior to the coronary sinus ostium. Likewise, the AV bundle is displaced posteriorly, is elongated, and courses along the lower rim of the VSD; this gives rise to the superior QRS axis seen on an electrocardiogram. With perimembranous VSDs, the AV bundle can be longer and is typically located along the posteroinferior rim of the defect. In single ventricle abnormalities, the locations of the AVN and AV bundle can vary widely.
Accessory pathways are accessory bundles of cardiomyocytes that electrically connect the atria and ventricles, providing the substrate for some supraventricular arrhythmias (as occurs in Wolff–Parkinson–White syndrome and Mahaim tachycardia) [92]. Right-sided pathways and some left-sided pathways run subendocardially. The most common locations in children are the left free wall and the posteroseptal right free wall [91]. Ebstein anomaly is frequently associated with Wolff–Parkinson–White syndrome and other accessory pathways.

Atrial conduction disturbances and arrhythmias are frequently related to sinus venosus myocardium and thus tend to take place at particular anatomical sites, such as the crista terminalis, ostia of the caval veins, coronary sinus, pulmonary veins, and the ligament of Marshall [92]. The structure of the AVN is complex, both anatomically and electrophysiologically, and in many normal hearts it provides the substrate (two pathways with different electrophysiological characteristics) for dual AVN physiology and AV nodal re-entry tachycardia (AVNRT).

At the molecular level, gene mutations that affect ion channels give rise to the cardiac channelopathies; the most important of these are long QT syndrome, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia, and short QT syndrome [93].

**KEY POINTS: DEVELOPMENT OF THE CONDUCTION SYSTEM**

- The primitive pacemaker is located at the junction of the sinus venosus and the primitive atrium.
- The AV node retains its primary phenotype of slow conduction allowing for appropriate AV delay, whereas the AV bundle, left and right bundle branches, and Purkinje fibers develop from fast-conducting ventricular myocardium.
- Abnormalities of the conduction system are expected in lesions that alter the AV concordance, proper alignment of the atrial and ventricular septa, and complete closure of the ventricular septum.

**Development of the aortic arches**

Blood vessels are formed by the aggregation of angioblasts (splanchnic mesoderm that has differentiated into endothelial cell precursors) into small endothelial-lined channels that connect to form vascular networks (vasculogenesis), which grow through the sprouting and branching of vessels (angiogenesis) [47]. Depending on the site of the vascular network, cells from the mesoderm, neural crest, or epicardium associate with the endothelial cells to form vascular smooth muscle, thereby stabilizing the vessel wall [94]. The dorsal aortae are bilateral, parallel, longitudinal channels that form in the mesoderm on either side of the notochord, adjacent to the ventral pharyngeal endoderm. The aortic sac is connected to the paired dorsal aortae by the artery of each pharyngeal arch; these vessels are referred to as pharyngeal arch arteries (PAA) or aortic arch arteries [9]. Pioneering work by Kirby, and later by Poelmann and Gittenberger-de Groot, demonstrated that cardiac neural crest cells migrate into the mesoderm of the pharyngeal arches (3, 4, and 6) and surround the endothelial cells to form the smooth muscle of the PAA [22,95–97]. The PAA are not all present simultaneously but form over time in a symmetric pattern cranially to caudally. The neural crest cells are critical for remodeling, whereby some segments of the aortic arch apparatus and dorsal aortae regress, while other segments transform and persist to produce the mature asymmetric pattern (Figure 4.18).

The dorsal aortae fuse in a caudal-to-cranial direction up to the seventh somite. The seventh somite is supplied by the seventh intersegmental artery, which forms the left subclavian artery and contributes to formation of the right subclavian artery. The dorsal aortae give off dorsal intersegmental arteries, which supply the spinal cord and developing somites [99]. Longitudinal anastomoses form between the intersegmental arteries, with those from the first to the seventh forming the vertebral artery. The first six intersegmental arteries regress after the vertebral artery is formed, and the vertebral artery arises from the seventh intersegmental artery, which itself forms part of the subclavian artery.

**Abnormalities of aortic arch development**

Abnormalities of the aortic arch occur when segments of the fourth aortic arch fail to regress or regression occurs at an abnormal site; this can be explained by Edwards’ hypothetical double aortic arch model (Figure 4.19) [100]. The aortic arch is referred to as left- or right-sided to indicate which mainstem bronchus is crossed by the arch [102]. The normal left aortic arch (LAA) results from regression of the segment of the right aortic arch between the right subclavian artery and the descending aorta. Conversely, a right aortic arch (RAA) with mirror-image branching is produced when the LAA regresses between the left subclavian artery and the descending aorta. An RAA with mirror-image branching is usually associated with cardiac malformations. A double aortic arch results from the persistence of both fourth aortic arches. Regression of the segment between the right carotid and right subclavian arteries results in an LAA with an aberrant right subclavian artery, whereas regression of the segment between the left carotid and left subclavian arteries results in an RAA with an aberrant left subclavian artery. An interrupted aortic arch (IAA) results from the regression of both the right and left fourth aortic arches. The most common type of IAA is type B, in which there is interruption between the left carotid and left subclavian arteries and normal regression of the right aortic arch. A vascular ring is an aortic arch anomaly in which the trachea and esophagus are completely encircled by vascular structures, which may be patent or consist of fibrous remnants, such as the ligamentum arteriosum. When the trachea and esophagus are not completely encircled, the abnormality is referred to...
Figure 4.18. Graphical representation of the arterial changes during transformation of the truncus arteriosus, aortic sac, pharyngeal arch arteries (PAAs), and dorsal aortas into the adult arterial pattern. Vessels not colored are not derived from these structures. (A) PAAs at 6 weeks; by this stage the first two pairs of PAAs have largely regressed; (B) PAAs at 7 weeks – the parts of the dorsal aortas and PAAs that normally regress are indicated with broken lines; (C) arterial arrangement at 8 weeks; (D) arterial vessels of a 6-month-old infant. Note that the ascending aorta and pulmonary arteries are considerably smaller at 8 weeks of development than in infancy, representing the relative flow through these vessels at the different stages of development. (Source: Moore et al. [98]. Reproduced with permission of Elsevier.)
as a vascular sling. Aortic arch anomalies can be associated with tracheobronchial and/or esophageal compression and, in the case of a pulmonary artery sling, malformations of the trachea [103].

Coarctation of the aorta is a focal narrowing of the aorta, usually consisting of a discrete posterior shelf or invagination just distal to the origin of the left subclavian artery opposite to the insertion of the ductus arteriosus (juxta-ductal). Coarctation is thought to be due to ducal tissue extending into the wall of the aorta or an abnormal flow pattern due to lesions, resulting in decreased flow into the ascending aorta. Thus, it is frequently associated with a bicuspid aortic valve, aortic stenosis, hypoplasia of the aortic arch, small left-sided structures, and VSDs.

Isolated PDA in full-term infants is most likely a congenital malformation with a genetic origin, with the persistent vascular structure having different histologic features from the normal ductus arteriosus [104]. A PDA may occur in isolation, particularly with prematurity, or in association with almost any other congenital cardiac anomaly. It is life-saving in some forms of CHD.

Figure 4.19 Diagram of Edward’s developmental model of the aortic arch. (A) Hypothetical double aortic arch system in which there is an aortic arch and ductus arteriosus on each side encircling the trachea (T) and esophagus (E), with the carotid and subclavian arteries arising bilaterally from the respective arches. The descending aorta is in the midline. (B) Normal arch branching results from interruption of the dorsal portion of the right arch between the right subclavian artery and descending aorta with regression of the right ductus arteriosus. AAo, ascending aorta; DAo, descending aorta; LCA, left carotid artery; LSA, left subclavian artery; PA, pulmonary artery; RCA, right carotid artery; RSA, right subclavian artery. (Source: Turkvatan et al. [101]. Reproduced with permission of the Korean Radiological Society.)

- Neural crest cells are critical for the development of the aortic arches.
- Abnormalities of the aortic arch occur when segments of the fourth aortic arch fail to regress or regression occurs at an abnormal site.

Development of the pulmonary and systemic veins

Pulmonary veins

The lungs and tracheobronchial tree develop from the respiratory diverticulum, a ventral outgrowth from the foregut. Early in development, the lungs have the same venous drainage as the foregut, namely via the splanchnic plexus into the cardinal and umbilicovitelline (systemic) veins (Figure 4.20).

The primary pulmonary vein develops by canalization within the dorsal mesocardium to form a channel [38]. Endothelial invagination from the left side of the primitive atrium into the dorsal mesocardium delineates the future orifice of the primary pulmonary vein [37]. This invagination is surrounded by right and left ridges of dorsal mesocardium, forming a pit (pulmonary pit) cephalad to the junction of the left and right horns of the sinus venosus and to the left of the developing septum primum. Further canalization of the primary pulmonary vein brings it into continuity with the cavity of the developing left atrium, and by the end of the first month of gestation, the primary pulmonary vein has established a connection between the pulmonary venous plexus of the lung bud and the sinoatrial portion of the heart. Once a connection has been

KEY POINTS: DEVELOPMENT OF THE AORTIC ARCHES

- During development, the initial arterial pattern becomes modified and some vessels regress completely, allowing for transformation into the definitive vascular pattern.
Figure 4.20 Development of the pulmonary veins. (A) At 27–29 days of gestation, the primordial lung buds are enmeshed by the vascular plexus of the foregut (splanchnic plexus). No direct connection to the heart is present at this stage. Instead, the multiple connections are present to the umbilicovitelline and cardinal venous systems. A small evagination can be seen in the posterior wall of the left atrium to the left of the developing septum secundum. (B) By the end of the first month of gestation, the common pulmonary vein establishes a connection between the pulmonary venous plexus and the sinoatrial portion of the heart. At this time, the connections between the pulmonary venous plexus and the splanchnic venous plexus are still patent. (C) Subsequently, the connections between the pulmonary venous plexus and the splanchnic venous plexus involute. (D) The common pulmonary vein (CPV) incorporates into the left atrium so that the individual pulmonary veins connect separately and directly to the left atrium. LA, left atrium; LCCV, left common cardinal vein; LLB, left lung bud; RA, right atrium; RCCV, right common cardinal vein; RLB, right lung bud; UV, umbilical vein. (Source: Brown et al. [108]. Reproduced with permission of Lippincott Williams & Wilkins.)

established between the primary pulmonary vein and the left atrium, the pulmonary venous plexus loses its connections with the systemic veins. Then, the common pulmonary vein incorporates into the left atrium so that the individual pulmonary veins connect separately and directly to the left atrium.

Abnormalities of pulmonary vein development

Total anomalous pulmonary venous connection (TAPVC) results from a failure to establish the normal connection between the common pulmonary vein and the pulmonary venous plexus before the connections with the splanchnic venous system regress. All the pulmonary veins join
a common horizontal or vertical vein behind the left atrium, which can drain via the supracardiac, cardiac, or infracardiac (infradiaphragmatic) route into the right heart circulation, producing a left-to-right shunt. Atresia of only the right or left portions of the common pulmonary vein before the connections with the splanchnic venous system regresses results in partial anomalous pulmonary venous connection (PAPVC) with drainage into derivatives of the left or right cardinal systems. Both TAPVC and PAPVC produce a left-to-right shunt and can be associated with pulmonary venous obstruction. Pulmonary veins can also be hypoplastic or atretic, with the most common variation in the number of pulmonary veins being a single pulmonary vein on either the right or left side (prevalence of about 24% in anatomic studies) [106]. Cor triatriatum is an oblique fibromuscular membrane that divides the left atrium into two chambers: a postero-superior chamber that receives the pulmonary veins and an antero-inferior chamber that communicates with the mitral valve and left atrial appendage [107]. Cor triatriatum is thought to arise from incomplete incorporation of the common pulmonary vein into the primitive left atrium. Sinus venosus ASDs are associated with drainage of some, and less frequently, all of the right pulmonary veins into the right SVC or right atrium and normal connection of the pulmonary veins to the left atrium. Congenital pulmonary vein stenosis typically occurs at the pulmonary vein–left atrial junction but can be progressive in the length and degree of stenosis and number of pulmonary veins affected. The embryologic basis for this anomaly appears to be abnormal incorporation of the common pulmonary vein into the left atrium [108]. Pulmonary veins may also be hypoplastic or atretic.

**KEY POINTS: DEVELOPMENT OF THE PULMONARY VEINS**

- The lungs and tracheobronchial tree develop from a ventral outgrowth of the foregut.
- Establishment of a normal connection between the primary pulmonary vein and the left atrium is linked to the loss of the initial connection of the pulmonary venous plexus to the systemic veins.
- Abnormalities of pulmonary vein development result from failure of normal connections between rudimentary pulmonary venous structures to be established before the connections with the splanchnic venous system regresses.

**Systemic veins**

By the end of the fourth week of development, the primitive venous system consists of three bilaterally symmetrical systems that each drain into the right and left horns of the sinus venosus: the vitelline veins, which drain the yolk sac and gastrointestinal derivatives and will develop into the portal system; the umbilical veins, which carry oxygenated blood from the placenta and disappear after birth, and the cardinal veins, which drain the head, neck, and body wall and will develop into the caval system (Figure 4.21). The shift of the systemic venous return to the right atrium is associated with regression and remodeling to yield the adult asymmetrical venous pattern [109].

The vitelline and umbilical veins are altered by the development of the liver in the septum transversum and the formation of the hepatic sinusoids. The vitelline veins pass from the foregut through the septum transversum and developing liver to connect with the hepatic sinusoids. When the left horn of the sinus venosus regresses to form the coronary sinus, the proximal (near the heart) left vitelline vein also regresses, causing blood from the left side of the abdominal viscera to be channeled to the right side with subsequent enlargement of the right vitelline vein. The portion of the right vitelline vein between the liver and heart becomes the suprahepatic (terminal) portion of the IVC. During the second and third months of gestation, the right vitelline vein inferior to the liver becomes the portal vein and superior mesenteric vein, and some of the left-to-right vitelline anastomoses become the splenic and inferior mesenteric veins.

The umbilical veins, which initially pass on either side of the liver, become connected to the hepatic sinusoids. The right umbilical vein regresses during the second month of gestation, whereas the left umbilical vein loses its connection to the left horn of the sinus venosus and forms a channel, the ductus venosus, which connects it to the right vitelline vein.

The anterior (superior) cardinal veins, which drain the cephalic part of the embryo, and the posterior (inferior) cardinal veins, which drain the remainder of the embryo, join to form the common cardinal veins, which enter the respective horns of the sinus venosus. During the eighth week of gestation, the proximal (terminal) portion of the right anterior cardinal vein and the right common cardinal vein form the SVC (Figure 4.22). An anastomosis develops between the left and right anterior cardinal veins to form the left brachiocephalic vein; the portion of the right anterior cardinal vein superior to the anastomosis will become the right brachiocephalic vein. The terminal portions of the left anterior and common cardinal veins regress. Although a large portion of the posterior cardinal veins regresses, the right and left subcardinal veins sprout from the base of the posterior cardinal veins and grow caudally [109]. The left subcardinal vein regresses, but the right subcardinal vein loses its connection with the posterior cardinal vein and joins with the right vitelline vein to form the portion of the IVC between the liver and kidneys (prerenal segment). The right and left supracardinal veins also sprout from the base of the posterior cardinal veins and receive drainage from the intercostal veins. Together with a portion of the posterior cardinal veins, the right and left supracardinal veins form the azygos vein on the right and the hemiazygos vein on the left. The right supracardinal vein also anastomoses with the right subcardinal vein to form the portion of the IVC below the kidneys (renal segment). The sacral segment of the IVC is derived from the right and left...
Figure 4.21 Primordial veins of the embryo. Illustration of the changes in the venous system that culminate in the adult venous pattern (ventral views). (A) At 6 weeks; (B) at 7 weeks; (C) at 8 weeks; (D) adult. (Sources: Arey [177] and Moore et al. [98]. Reproduced with permission of Elsevier.)
posterior cardinal veins and the sacral segment connecting them. Thus, the IVC is made up of elements from four separate venous systems: the right vitelline vein between the liver and heart; the right subcardinal vein between the liver and kidneys; the right supracardinal vein below the kidneys; and the right and left posterior cardinal veins with the sacral segment connecting them.

Abnormalities of systemic vein development
The complex development of the venous system results in a wide spectrum of systemic venous anomalies. Heterotaxy syndrome results from disorders of left-right axis determination during early embryonic development and is frequently associated with systemic venous abnormalities [110]. Failure of the left anterior and left common
cardinal veins to regress results in a persistent left SVC (LSVC), the prevalence of which is higher in patients with CHD. An LSVC may be found in association with a right SVC (bilateral SVCs) or may be the only SVC if the right anterior and right common cardinal veins have regressed. An LSVC will drain normally into the right atrium via the coronary sinus in the majority of cases, but it will drain into the left atrium if the coronary sinus is partially or completely unroofed [111]. Bilateral SVCs with an unroofed coronary sinus usually occur in association with other congenital heart defects.

Failure of the hepatic segment of the IVC to form results in an interrupted IVC with azygos continuation into the right or left SVC; the hepatic veins in this setting drain directly into the right atrium. Multiple variations of bilateral IVCs can occur.

### Key Points: Development of the Systemic Veins

- The primitive systemic venous system consists of three bilaterally symmetrical systems: the vitelline veins, the umbilical veins, and the cardinal veins.
- The shift of the systemic venous return to the right atrium is associated with regression and remodeling, resulting in the adult asymmetrical venous pattern.
- Alterations in the complex development of the venous system lead to a wide spectrum of systemic venous anomalies.

### Innervation of the Developing Heart

The heart has both sensory (afferent) and motor (efferent) innervation, which is well described by Hildreth et al. and Kirby (Figure 4.23) [112,113]. Sensory information is relayed from the heart to the brain via both parasympathetic and sympathetic nerve pathways. One set of afferent nerves travels with the vagus nerve via the nodose ganglion (inferior ganglion of the vagus nerve) to the nucleus of the solitary tract in the brainstem. A second set of sensory nerves travels with the sympathetic nerves to the dorsal root ganglion and spinal cord. The parasympathetic afferents play a role in controlling both sympathetic and parasympathetic output, whereas the sympathetic afferents do not have any tonic influence over autonomic activity but are mostly nociceptive, as they are activated by coronary occlusion and register cardiac pain.

The motor (efferent) pathways are part of the autonomic nervous system, and both the parasympathetic and sympathetic pathways use preganglionic to postganglionic relays. Parasympathetic preganglionic neurons originate from the nucleus ambiguous and dorsal motor nucleus of the vagus in the medulla oblongata and use the vagus tracts to connect with postganglionic relays in the cardiac ganglia. Sympathetic preganglionic neurons originate in the intermediolateral column in the thoracic spinal cord and synapse with postganglionic neurons in the ganglia of the lower cervical and upper thoracic sympathetic chain. All of the postganglionic autonomic neurons are derived from the neural crest [113]. Parasympathetic postganglionic neurons originate in the neural crest between the mid-otic placode and somite 3, and migrate through the pharyngeal arches to the cardiac plexus and cardiac ganglia. Sympathetic postganglionic neurons originate in the trunk neural crest and also contribute to the primary sympathetic chain and dorsal root ganglia.

The cardiac plexus is an accumulation of mixed neurons, both efferent and afferent. It is located cranial to the heart and surrounds the aortic arch and great vessels. Although it is initially symmetrical, in the adult there is a right cardiac plexus surrounding the innominate artery and a left cardiac plexus around the aortic arch [114]. The cardiac ganglia are located in the cardiac plexus and widely distributed on the surface of the heart. Parasympathetic ganglia are found around the SAN, around the bases of the vena cavae and pulmonary veins, near the AVN, in the atrial septum, in the atrial appendages, in the posterior AV groove, at the base of the pulmonary trunk and aorta, and at the origins of the left and right coronary arteries [113]. Parasympathetic control of cardiac rate and conduction are controlled by one set of ganglia near the SAN and by a separate set of ganglia at the junction of the IVC and inferior left atrium, respectively [11,115].

The cardiac nervous system develops and matures slowly, and is not fully functional until well after birth [113]. Parasympathetic innervation precedes sympathetic innervation, so the parasympathetic–cholinergic system becomes functional before the sympathetic–adrenergic system. Autonomic receptor-mediated effector mechanisms are present before functional innervation, thereby allowing a cardiac response to circulating catecholamines to mitigate the effects of hypoxia and bradycardia [116].
Parasympathetic fibers are found throughout the atrial myocardium but are scarce in the ventricles, whereas sympathetic fibers are found throughout the atria and ventricles. The primary neurotransmitter of the parasympathetic neurons is acetylcholine, whereas that of the sympathetic neurons is norepinephrine.

**Abnormalities of cardiac innervation**

*Dysautonomias* result from impaired autonomic interactions due to inadequate development, migration, survival, and function of sensory and autonomic neurons; the sympathetic neurons are affected more often than the parasympathetic neurons [117]. *Familial dysautonomia* (Riley–Day syndrome) is the best known of the hereditary sensory and autonomic neuropathies and is associated with orthostatic hypotension and an increased risk of sudden death. It is caused by mutations of the IKAP gene on chromosome 9q31 and is associated with catecholamine hypersensitivity [118].

*Sudden infant death syndrome* has been linked to abnormal development of the autonomic nervous system, resulting in immature cardiorespiratory autonomic control and failure of the arousal responsiveness from sleep [119].

Autonomic dysfunction is likely a factor in Down syndrome, because the heart rate and blood pressure responses to exercise are reduced [120,121] and the risk of bradycardia is increased during induction of anesthesia [122].

### Table 4.1 Stages of human development with corresponding events in cardiac development

<table>
<thead>
<tr>
<th>Carnegie stage</th>
<th>Human DPC</th>
<th>Mouse DPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>CS8</td>
<td>17–19</td>
<td>7</td>
</tr>
<tr>
<td>CS9</td>
<td>19–21</td>
<td>7.5</td>
</tr>
<tr>
<td>CS10</td>
<td>22–23</td>
<td>8</td>
</tr>
<tr>
<td>CS11</td>
<td>23–26</td>
<td>8.5</td>
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<tr>
<td>CS12</td>
<td>26–30</td>
<td>9.5</td>
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<tr>
<td>CS13</td>
<td>28–32</td>
<td>10.5</td>
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<tr>
<td>CS14</td>
<td>31–35</td>
<td>11.5</td>
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<tr>
<td>CS15</td>
<td>35–38</td>
<td>12</td>
</tr>
<tr>
<td>CS16</td>
<td>37–42</td>
<td>12.5</td>
</tr>
<tr>
<td>CS17</td>
<td>42–44</td>
<td>13.5</td>
</tr>
<tr>
<td>CS18</td>
<td>44–48</td>
<td>14.5</td>
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<tr>
<td>CS19</td>
<td>48–51</td>
<td>15</td>
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<tr>
<td>CS21</td>
<td>53–54</td>
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<tr>
<td>CS22</td>
<td>54–56</td>
<td>16.5</td>
</tr>
<tr>
<td>CS23</td>
<td>56–60</td>
<td>17.5</td>
</tr>
</tbody>
</table>

DPC, days post coitum.

Source: adapted from Sylva M et al. [24] with permission.
the information discussed in this section of the chapter [24]. Four cell lines (cardiomyocytes, endocardium, epicardium, and endothelium) are derived from the mesoderm to form the building blocks of the heart and vascular system (Figure 4.24) [23]. Cardiac neural crest cells are critical to the formation and remodeling of the aortic arch arteries, outflow tract septation, semilunar valvulogenesis, cardiac neuronal tissue, and the insulation of the conduction system [51]. Reactivation of cardiac stem cells has opened the door for using regenerative medicine and novel therapies for treating congenital and acquired heart disease [10,123].

**Nomenclature for congenital heart disease**

It is well known that the large number, wide spectrum, and complex nature of congenital malformations of the cardiovascular system can make it challenging to understand the corresponding structural abnormalities and their associated functional and hemodynamic consequences. This issue can be further complicated by the seemingly bewildering nomenclature and classification systems used in congenital and pediatric cardiology. In addition, the diverse terminology (at times, different terms can even be used to refer to the same anatomic structure, pathologic finding, or lesion) and the numerous classification schemes for categorizing individual anomalies can pose obvious difficulties [124,125]. This variable taxonomy can be confusing for many, but it is even more perplexing for individuals with limited knowledge or familiarity with the subject, further adding to the intimidating aspects of CHD.

Many clinicians have acknowledged the critical need for a consistent nomenclature and classification system for CHD that can be widely accepted by all disciplines involved in the care of these patients. As far back as the late 1970s, Shinebourne et al. [126] indicated that “for a nomenclature system to be of value, it needed to be capable of describing any combination of cardiac malformations which may be encountered”. It was also noted that the scheme “should allow for precise classification of such malformations during a patient’s life.” Despite numerous efforts to create such a classification system, work in this area is still ongoing many years later. The lack of a uniform classification scheme for CHD or a consistent nomenclature for describing the various defects continues to be a source of frustration and confusion in everyday practice. However, some individuals recognize that the likelihood of implementing a single, universally accepted system is remote, and they continue to see merits in the various schemes currently used.

In the late 1990s, the Society of Thoracic Surgeons, in collaboration with The European Association for Cardiothoracic Surgery, launched the International Congenital Heart Surgery Nomenclature and Database Project with the hope of standardizing the nomenclature used for CHD. One goal was to establish a foundation to facilitate multi-institutional analysis of patient outcomes. This effort led to the adoption of a common nomenclature system by these professional organizations [127]. Concurrently, another international nomenclature system, the European Paediatric Cardiac Code, was developed for congenital cardiac disease [128,129]. In 2000, The International Nomenclature Committee for Pediatric and Congenital Heart Disease was created, which evolved into a society with various components, including a Nomenclature Working Group. As a result, the International Pediatric and Congenital Cardiac Code (IPCCC) was eventually developed, which allowed for cross-mapping of the two nomenclature systems for CHD [130]. The aim of the project was to provide an all-inclusive, internationally accepted, cohesive, and comprehensive system for describing pediatric cardiovascular diseases and CHD using a common nomenclature (www.ipccc.net). This undertaking would ultimately enhance communication among healthcare providers; facilitate education, research, and patient care; and allow for multicenter assessment of clinical outcomes, risk stratification, and many other important benefits. In fact, the IPCCC nomenclature, in conjunction with the database created by the International Congenital Heart Surgery Nomenclature and Database Project, has been used in recent years in extensive surgical outcome analyses involving large numbers of patients. The reader is referred to various publications related to these projects, which address the nomenclature for specific defects [131–144].

**Sequential segmental approach to diagnosis**

The *sequential segmental approach* is considered the essence of the diagnostic assessment for CHD. For many decades, this system has been used to characterize congenital anomalies that affect the heart and related vascular structures. Several publications have addressed, in detail, the applications of this analysis in the diagnosis of CHD and the steps involved in a comprehensive structural assessment [126,145–152]. The segmental approach, as initially described by Richard Van Praagh and colleagues [153,154] in the 1960s, relies upon an examination of cardiac anatomy in a series of segments or “building blocks.” These major units are considered the essential components of the heart, whether normal or diseased [150]. The anatomy of the various cardiac segments and their relationships to each other represent the foundation of the segmental analysis. Robert Anderson and colleagues [145,146] expanded upon this concept but reduced the emphasis on relationships by proposing a scheme based on blood flow through the heart, which focused on characterizing the connections between the segments (i.e., a sequential segmental approach).

The detailed methodology used in the sequential segment-by-segment approach allows for a stepwise examination of all cardiac segments by navigating through the heart in the direction of blood flow from the atria to the ventricles to the great arteries. The three main segments
Chapter 4 Development of the Cardiovascular System and Nomenclature for CHD 71

Figure 4.24 Schematic presentation of cellular contribution to heart development with special focus on role of epicardium and epicardially derived cells (EPDCs) during normal development, disease, and repair processes. Four mesodermal cell lines (cardiomyocytes, endocardium, epicardium, and endothelium) are considered to form the main building blocks of the heart. The differentiation of each line is depicted together with the main interactions with the other cell lines. The most frequent EPDC-related congenital malformations and (acquired) disease processes are boxed in green, while three cardiac (stem) cell populations that may become reactivated are presented on the far right. (Source: Gittenberger-de Groot et al. [23]. Reproduced with permission of Elsevier.) aPEO, arterial proepicardial organ; vPEO, venous proepicardial organ; a-epicardium, arterial epicardium (from aPEO); c-epicardium, complete epicardium (from vPEO); VSMCs, vascular smooth muscle cells; CMPCs, cardiomyocyte progenitor cells; ECs, endothelial cells

are the veins and atria, ventricles, and great arteries. The units are joined to each other by two connecting cardiac segments (or junctions): the AV junction (AVC region), which connects the atria to the ventricles, and the VA junction (infundibulum/conus arteriosus), which connects the ventricles to the great arteries (Figure 4.25). This systematic examination is an organized and rigorous method that facilitates the defining of congenital cardiovascular defects. The benefit of this analysis is that it can be applied to all congenital cardiac malformations, although it is particularly useful for characterizing complex defects. The merits of this approach are reflected in the fact that this system has been incorporated into clinical use within various disciplines related to CHD and applied in the evaluation of fetuses to adults [155–162].

Historically, and based on the development of the nomenclature, there have been two major philosophies regarding the segmental assessment of the congenitally malformed heart. These schools of thought have been led by two world-renowned leaders in the field: Drs. Richard Van Praagh and Robert H. Anderson. Colloquially, these have been referred to as the ‘Van Praaghian’ and ‘Andersonian’ approaches, and clinicians have generally been divided as followers of the teachings of one school or the other. However, many practitioners have opted for a stance somewhere in the middle [163]. Although these approaches share common elements, there are many important differences. One significant difference is related to the shorthand notation used in the Van Praagh system, as described later in this chapter. Other divergent viewpoints include terminology and the methods used to describe morphology. The disparities between the two major schools of nomenclature have created disagreements among advocates and specialists in the field, sometimes resulting in heated arguments and controversies. Efforts have been made to reconcile these two approaches in recognition of the fact that both of these systems have virtues and that, in many ways, they complement each other [164,165]. It should be emphasized that regardless of the nomenclature or scheme favored, it is more important
that each institution has a uniform and consistent approach for describing and referring to the various defects or structural abnormalities to optimize communication among all providers involved in patient care.

The Van Praagh notation

A unique feature of the Van Praagh style is the use of a three-letter notation, or code, enclosed in braces or curly brackets [X,X,X]. The letters in the set are abbreviations that represent the sidedness or anatomical organization (referred to as “situs”) of the three main cardiac segments of the heart in venoarterial sequence (atria, ventricles, great arteries)[124,151]. The different possibilities for each segment are denoted by different letters. This shorthand system does not specify the “alignments” (AV and VA) between the cardiac segments, a term preferred by Van Praagh over “connections” to describe the segments between the atrial and ventricular chambers, and the ventricles and great arteries. In this system the segmental alignments are noted separately [151,152, 166]. Significant abnormal VA alignments are noted before the braces, while important segmental connections and other associated cardiovascular malformations are listed after the braces [124].

At first glance, this nomenclature system may appear relatively straightforward and easy to understand; however, the combination of letters can be somewhat complex to decode or interpret, particularly for individuals who are not familiar with the shorthand nomenclature. In addition, although the segmental classification scheme can be used to describe most congenital heart defects, some anomalies, such as heterotaxy syndromes, can be difficult to define precisely using this scheme. Therefore, even though it is well recognized and widely applied, this system has not been universally embraced. Some consider a more descriptive approach less likely to cause confusion, particularly, in the case of complex CHD[167].

KEY POINTS: SEQUENTIAL SEGMENTAL APPROACH TO DIAGNOSIS

- The sequential segmental approach is the essence of diagnostic assessment for CHD.
- This approach allows for a stepwise examination of all cardiac segments by navigating through the heart in the direction of blood flow.
- There are two major philosophies regarding the segmental assessment of the congenitally malformed heart: one led by Dr. Richard Van Praagh and the other by Professor Robert H. Anderson.
- In the Van Praagh notation the letters are abbreviations that represent the sidedness or anatomical organization (referred to as situs) of the three main cardiac segments of the heart in venoarterial sequence (atria, ventricles, great arteries).
- Numerous efforts have attempted to create a single classification/nomenclature system in CHD; however, work in this area is still ongoing.

Morphologic and segmental anatomy

An understanding of the elements considered in the morphologic assessment of the heart and the various congenital anomalies that affect the cardiovascular system is important for the practice of pediatric/congenital cardiac anesthesia. This section of the chapter provides a brief overview of the essential aspects of evaluating the anatomy of the cardiovascular system. It covers the sequential segmental analysis in general and other relevant components of the diagnostic assessment of the congenitally malformed heart, but it does not dwell on the specifics of one language or taxonomy over the other for describing CHD. Thus, the discussion is not meant to be comprehensive but, instead, aims to highlight important steps involved in the anatomic evaluation of a patient with CHD.

Cardiac position and apex orientation

This aspect of the CHD evaluation can be confusing because it is described differently by various sources. One approach describes the cardiac position as the spatial location of the majority of the cardiac mass within the thoracic cavity, using the sternum as the midline reference. The term levocardia indicates that the heart occupies most of the left hemithorax (i.e., a left-sided heart), dextrocardia indicates that the heart is in the right hemithorax (i.e., right-sided heart), and mesocardia indicates that the heart is in the midline position. In addition, a distinction is made between primary and secondary dextrocardia; the former is due to a structural cardiac defect, whereas the latter results from the heart being displaced by extracardiac conditions.

An alternative algorithm specifies both cardiac position and orientation, as these are not to be considered...
In the human body, there are distinct left-sided and right-sided structures as discussed in earlier sections of this chapter on development of the cardiovascular system [168]. In the normal arrangement, the liver and cecum are on the right side of the body, whereas the stomach and spleen are on the left. There is also a distinctive pattern to each lung in terms of lobes, anatomy of the bronchi, and course of the bronchi with respect to the associated pulmonary artery. The normal anatomic layout is characterized as follows: the right lung comprises three lobes, a short mainstem bronchus, and a course of the bronchus above the right pulmonary artery (eparterial), whereas the left lung comprises two lobes and a longer mainstem bronchus (as compared with the right bronchus) that courses below the left pulmonary artery (hyparterial).

The normal (usual) arrangement of the thoraco-abdominal organs is referred to as visceral situs solitus. In contrast, the mirror image arrangement, in which the left–right position and orientation of the organs is reversed, is referred to as visceral situs inversus. A third type of arrangement is referred to as situs ambiguous (Latin spelling; the term “situs ambiguous” commonly used, as in this chapter), which is defined in Van Praagh’s school as “an abnormality in which there are components of situs solitus and situs inversus in the same person” [134]. In both situs solitus and situs inversus, an asymmetric pattern of the abdominal/thoracic organs is present. In contrast, in situs ambiguous there is symmetry of the abdominal/thoracic organs, but their position/orientation is variable. It has been proposed that “situs ambiguous can be considered to be present when the thoracic and abdominal organs are positioned in such a way with respect to each other as to be not clearly lateralized and thus have neither the usual, or normal, nor the mirror-imaged arrangements” [134]. When this arrangement occurs, there is a tendency towards duplication of either right-sided or left-sided structures. This abnormal anatomic organization is frequently found within the context of heterotaxy, which is defined as “an abnormality where the internal thoraco-abdominal organs demonstrate abnormal arrangement across the left-right axis of the body” [134]. In heterotaxy syndromes, a spectrum of cardiac and extracardiac anomalies can be present, including absence of lateralization of the abdominal viscera, lack of a spleen or presence of multiple spleens (asplenia and polysplenia syndromes), and rotation defects of the gastrointestinal system, among other defects.

Atrialsitus is a term used to describe the arrangement of the atria as determined by the position of the morphologic right and left atria. To evaluate the atrial situs, one must first morphologically identify the atrial chambers (process described in the following section). The visceral anatomy may be used as an aid when defining atrial morphology because the atrial situs usually follows that of the viscera. Once the atrial chambers are identified, their arrangement (atrial situs) is defined (Figure 4.26). In atrial situs solitus (the normal arrangement), the morphologic right atrium is to the right of and anterior to the morphologic left atrium.

**KEY POINTS: CARDIAC POSITION AND APEX ORIENTATION**

- Cardiac position refers to the spatial location of the majority of the cardiac mass within the thoracic cavity.
- Cardiac orientation refers to the alignment from the base (great arteries) to the apex (ventricular apex).
- In most cases, the cardiac position and base-to-apex orientation are in agreement.

**Visceral and atrial situs**

The first step of the sequential analysis, before defining the cardiac structures, is evaluating the anatomic relationships of the viscera (i.e., the abdominal and thoracic organs). This is referred to as determining the visceral situs, or pattern of anatomic organization (meaning sidedness). In clinical practice, to determine the visceral situs, the abdominal viscera are examined, focusing on the position of the liver, stomach, spleen, and abdominal great vessels (i.e., the aorta and IVC). This examination is primarily performed using ultrasonography. The situs of the thorax can be evaluated by assessing bronchial morphology, as determined, for example, by chest radiography.
In atrial situs inversus, the morphologic right atrium is to the left of and anterior to the morphologic left atrium. In atrial situs ambiguous, it is not feasible to clearly define the atrial sidedness.

The approach by Anderson classifies the atrial arrangements into four types based on the morphology of the atrial appendages. Two of these variants fall within the category of isomerism, a term used to describe symmetry of a body structure or a mirror-image arrangement, in this case the atrial appendages. The four possible arrangements of the atrial chambers are usual (normally arranged or situs solitus), mirror-imaged (situs inversus), and – when both appendages have either right or left morphologic characteristics – the pathologic variants are referred to as either right or left atrial isomerism, respectively (Figure 4.27) [169–171]. Although the concept of isomerism as it relates to cardiac structures has been debated [172], the term is ubiquitous in day-to-day CHD parlance. The two distinct isomeric atrial arrangements are usually considered under the category of situs ambiguous, although it has also been contended that these patterns are not, in fact, ambiguous [145]! These atrial arrangements are associated with isomerism of the thoracic organs; right isomerism is usually found with asplenia, and left isomerism is found with polysplenia [173].

Because the atrial situs rarely differs from the visceral situs, as previously indicated, one may refer to this as the visceroatrial situs (Figures 4.28 and 4.29). In the Van Praagh shorthand notation [174], the types of visceroatrial situs are denoted as “S” for situs solitus, “I” for situs inversus, and “A” for situs ambiguous. Van Praagh has emphasized that the term situs ambiguous denotes that the visceroatrial situs is anatomically uncertain or indeterminate – as such, it is not a distinct or third type of situs, but rather a term used to indicate that the type of visceroatrial situs cannot be defined. As discussed under visceral situs ambiguous, this situs is usually seen in children with heterotaxy syndrome. In bilateral right-sidedness, or right visceroatrial isomerism, the atria, lungs, and bronchi are morphologically right-sided. Conversely, in bilateral left-sidedness, or left visceroatrial isomerism, the atria, lungs, and bronchi are morphologically left-sided. It must be emphasized that organ location, or situs, can differ, and discordance of the situs of different organs can exist.

**KEY POINTS: VISCERAL AND ATRIAL SITUS**

- The initial step of the sequential analysis involves assessing the visceral situs or anatomic relationships of the thoracoabdominal organs.
- The atrial situs rarely differs from the visceral situs.
- The three types of visceroatrial situs are situs solitus (normal arrangement), situs inversus (mirror image arrangement), and situs ambiguous.
- In both situs solitus and situs inversus, there is asymmetry in the pattern of the abdominal/thoracic organs; by contrast, in situs ambiguous, a symmetric pattern is present with a tendency towards duplication of either right-sided or left-sided structures.
- Visceral situs ambiguous is usually associated with heterotaxy syndrome.
Great veins and atria

The structures most frequently considered under the subject heading of great veins are the vena cavae, pulmonary veins, and coronary sinus. **Systemic venous drainage** in the normal heart is via the SVC and IVC. These right-sided structures drain into the right atrium. The coronary sinus receives blood from the cardiac veins and empties into the floor of the right atrium, near the inferior aspect of the atrial septum and the orifice of the IVC. **Pulmonary venous drainage** is via the upper and lower right- and left-sided pulmonary veins. Venous variants (e.g., left SVC to the coronary sinus) or anomalies (e.g., interrupted IVC with azygous continuation or anomalous pulmonary venous connections) may co-exist with other defects in CHD; therefore, a complete anatomic examination should include an assessment of these structures to determine primarily their presence, patency, and sites of drainage.

Anatomic landmarks are the primary criteria used to identify and distinguish between the atrial chambers (Box 4.1). In a **morphologic right atrium**, the trabecular portion (pectinate muscles) extends from the crista terminalis to the base of the atrial appendage. A smooth sinusual portion is present between the crista terminalis and atrial septum. The septal aspect of the right atrium displays the superior and inferior limbic bands of the fossa ovalis. The limbus is a thick muscular structure that can be used to identify the right atrium. The right atrial appendage has a broad base and a blunt tip (i.e., triangular shaped). In contrast, the **morphologic left atrium** has a smooth wall, and the left atrial appendage is narrow and elongated, or “finger-like.” The septal aspect displays the thin valve of the foramen ovale. In the sequential segmental approach proposed by Anderson, the morphology of the atrial appendages is used as the foundation for identifying the atrial chambers.

Box 4.1: Morphologic features of the right and left atria

**Right atrium**
- Broad-based (triangular-shaped) appendage
- Internal free wall has crista terminalis (also known as terminal crest) which is the boundary between the smooth-walled posterior aspect and the muscular anterior aspect of the chamber
- Extension of pectinate muscles toward the atrioventricular valve
- Septum secundum (limbus of the fossa ovalis)
- Normally receives superior and inferior vena cavae and the coronary sinus

**Left atrium**
- Long and narrow (finger-like) appendage
- Smooth posterior surface receiving pulmonary veins, no crista terminalis
- Pectinate muscles contained within the appendage
- Septum primum (flap valve of the foramen ovale)
- Normally receives the pulmonary veins

The right atrium normally receives blood from the vena cavae and coronary sinus, and the left atrium receives blood from the pulmonary veins. However, as the systemic and pulmonary venous drainage may be variable and/or anomalous, as previously indicated, these criteria cannot be relied upon to definitively determine atrial morphology. Although the morphology of the atrial appendages is frequently used to define the atria and, therefore, the atrial situs, as noted, because the shape of the appendages may be subject to changes under various conditions, concern has been raised as to whether atrial appendage morphology is a reliable marker for identifying atrial structures and distinguishing between them [175].

The anatomic evaluation of the atria includes assessment of the interatrial septum and related areas for communications that may allow for atrial level shunting.
and the evaluation of pathology/variants that may be associated with structures such as the appendages and atrial cavities.

KEY POINTS: GREAT VEINS AND ATRIA

- In the normal heart, systemic venous drainage is via the SVC and IVC into the right atrium and pulmonary venous drainage is via the right- and left-sided pulmonary veins into the left atrium.
- Anatomic landmarks are the primary criteria used to identify and distinguish between the morphologic right and left atria.
- Because systemic and pulmonary venous drainage may be variable and/or anomalous, these criteria cannot be relied upon to definitively determine atrial morphology.
- The anatomic evaluation of the atria includes assessment of the interatrial septum and the cavities to evaluate for pathology.

Ventricles and ventricular septum

An analysis of the ventricular segment includes determining the type of ventricular loop (topology or handedness of the ventricular mass; also referred to as describing the chirality) and the relative spatial relationship between the ventricles and the atria. Ventricular looping, as discussed in earlier portions of this chapter, can result in either D-loop (right-handed topology) or L-loop (left-handed topology) ventricles. In the normal D-loop heart, the morphologic right ventricle is right-handed and the morphologic left ventricle is left-handed, whereas in the L-loop heart, the morphologic right ventricle is left-handed and the morphologic left ventricle is right-handed (Figure 4.30). L-looping of the ventricles may also be referred to as ventricular inversion. The types of ventricular situs (loop or topology) have been described in the Van Praagh system [174] as follows: solitus or D-loop ventricles (D); inverted or L-loop ventricles (L); and ambiguous or X-loop ventricles, where X indicates unknown situs (looping cannot be determined).

The ventricles are defined by their anatomy and not by where they are spatially located. Ventricular morphology is used to identify the ventricles and, therefore, their location (Box 4.2). The right ventricle is triangular-shaped in nature and characterized by a trileaflet AV valve (tricuspid valve), consisting of septal, anterior, and posterior leaflets. The tricuspid valve inserts inferiorly onto the interventricular septum relative to the mitral valve and is termed septophilic because of its septal leaflet attachments to the interventricular septum. The densely trabeculated right ventricle consists of several papillary muscles. The pulmonary valve rests on a muscular infundibulum above the tricuspid valve. In contrast, the left ventricle is shaped similarly to a bullet ellipse and is characterized by a bileaflet AV valve (mitral valve), consisting of anterior and posterior leaflets. There are no mitral valve attachments to the interventricular septum; therefore, the valve is referred to as septophobic. The left ventricle has a smooth wall (fine trabeculations) and contains two prominent papillary

Figure 4.30 Ventricular topology. The figure shows how the position of the palmar surface of either the right hand (A) or the left hand (B) can be oriented over the septal aspect of the morphologic right ventricle (thumb over the ventricular inlet and fingers over the ventricular outlet), corresponding to D-loop (right-hand topology) or L-loop (left-hand topology). (Source: Ms. Gemma Price. Reproduced with permission.)
The ventricular septum separates the right and left ventricles. A VSD is an opening or gap in the ventricular septum. This is one of the most common intracardiac defects and also the most common type of CHD requiring surgery. These defects vary in size, shape, and location and can occur anywhere in the ventricular septum as single or multiple entities. They are classified into various types depending on their location (Figure 4.31). The evaluation of the ventricular septum is complicated by the fact that this structure is not a straight wall that divides the ventricles but rather a three-dimensional structure that includes the membranous, muscular (also known as trabecular), infundibular, inlet, and AV segments. Characterizing these defects requires a detailed, systematic examination.

**Box 4.2: Morphologic features of the right and left ventricles**

**Morphologic right ventricle**
- Trileaflet atrioventricular (tricuspid) valve with septal leaflet attachments to the interventricular septum (septohilic)
- Atrioventricular (tricuspid) valve more apically positioned on the interventricular septum when compared with the mitral valve
- Coarse muscular trabeculations at the apical portion
- Presence of moderator band and septomarginal trabeculation (characteristic muscle band on the septal aspect)
- Tricuspid valve is separated from the pulmonary valve by the crista supraventricularis (supraventricular crest) or infundibulum
- Chamber shaped like a cone

**Morphologic left ventricle**
- Bileaflet atrioventricular (mitral) valve without septal attachments (septohilic)
- Atrioventricular (mitral) valve with superior insertion to the interventricular septum, as compared with the tricuspid valve
- Smooth muscular trabeculations at the apical portion
- Absence of moderator band, presence of paired papillary muscles
- Mitral valve in fibrous continuity to aortic valve (infundibulum absent)
- Chamber shaped like a cone

**Key Points: Ventricles and Ventricular Septum**
- Analysis of the ventricular segment involves determining the type of ventricular loop and the relative spatial relationship between the ventricles and the atria.
- Ventricular looping can result in D-loop (right-handed) or L-loop (left-handed) ventricular topology.
- The ventricles are defined by their anatomy and not by where they are spatially located; ventricular morphology is used to identify the ventricles and, therefore, their location.
- The ventricular septum is a three-dimensional structure comprising various segments, implying complexity in its evaluation and in examining interventricular communications.

**Atrioventricular junction**
The AV canal, or AV junction, consists of the AV valves and AV septum.

**Atrioventricular valves**
An important aspect of the evaluation for CHD is an assessment of the AV valves (tricuspid and mitral valves). This analysis includes determining valvular patency, leaflet morphology (size, number, and commissures), annular dimensions and orifice shape, in addition to evaluating chordal structures and papillary muscles that comprise the support apparatus. Other features of the AV valves that are of interest include the point of septal insertion at the annulus and the presence/absence of chordal attachments to the ventricular septum. As indicated previously, these features facilitate the morphologic identification of the ventricles because the AV valves are always associated with their respective ventricles (i.e., the tricuspid valve with the right ventricle and the mitral valve with the left ventricle).

**Atrioventricular connections**
To ascertain the connection between the atria and ventricles, or the sequence of these structures, it is necessary to first fully analyze each of these segments and identify the chambers. Several AV connections/alignments may be possible, as depicted in Figure 4.32. The AV connection can either be biventricular or univentricular. Biventricular connections can be classified into either concordant or discordant. A concordant AV connection implies that the normal anatomic relationship exists, meaning the morphologic right atrium connects to the morphologic right ventricle and the morphologic left atrium connects to the morphologic left ventricle. In the case of a discordant AV connection, the morphologic right atrium opens into the morphologic left ventricle and the morphologic left atrium opens into the morphologic right ventricle [166]. Examples of cardiac defects in which the AV relationship is discordant include corrected transposition (characterized by both AV and VA discordance) and isolated ventricular inversion (AV discordance and VA concordance). The term univentricular AV connection is used when only one ventricle is connected to the atrial chamber. In children with a single ventricle, the AV relationship may differ.

The presence of concordant or discordant AV connections is independent of ventricular position, meaning that either connection can be seen in situs solitus or situs inversus. In the sequential analysis, the AV connection/
Figure 4.31 Segments of the ventricular septum. Diagrammatic illustration of the various segments of the ventricular septum as viewed from the left ventricle (A) and along the length of interventricular septum (B): membranous (MS), infundibular (IS), trabecular (TS), inlet (IS), and atrioventricular (AVS) septum. AV, aortic valve; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. (Source: Ammash [176]. Reproduced with permission of the American Heart Association.)

Figure 4.32 Atrioventricular alignments/connections. Diagrammatic representation of potential atrioventricular (AV) alignments and connections. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. (Source: Geva [105]. Reproduced with permission of Wiley.)
alignment can also be described as **common** (common AV valve), **double inlet** (double-inlet left ventricle), **absent** (AV valve atresia), **overriding**, or **straddling** (Figure 4.32).

**KEY POINTS: ATRIOVENTRICULAR JUNCTION**

- An important aspect of morphologic evaluation in CHD is the assessment of the AV valves.
- The AV valves are always associated with their respective ventricles.
- To determine the AV connections or sequence of anatomic structures, each of the chambers should be identified first.
- The AV connection can be either biventricular or univentricular; biventricular connections can be classified into either concordant or discordant.
- The presence of concordant or discordant AV connections is independent of ventricular position

**Ventriculoarterial junction**

The VA junction (infundibulum/conus arteriosus) is the cardiac segment that connects the ventricles to the great arteries. Various aspects of this connection should be considered during a morphologic evaluation, as explained in the following sections.

**Conal or infundibular anatomy**

The distal region of the conus arteriosus, identified by the muscular infundibulum, is normally found immediately underneath the pulmonary valve, separating the tricuspid valve from the pulmonary valve. In contrast, there is fibrous continuity between the mitral and aortic valves (mitro-aortic continuity), and no intervening muscular tissue is present in the normal heart. An important element to include when describing cardiac anatomy is the morphology of the infundibulum, or outlet portion of the ventricles, which occurs essentially in four different anatomic types. These are depicted in Figure 4.33. In the normal heart, as previously noted, the infundibulum is in the subpulmonary location. Alternatively, the muscular infundibulum may be in the subaortic location (e.g., in D-transposition of the great arteries), bilateral (e.g., in a double-outlet right ventricle), or deficient/absent (e.g., in the rare case of a double-outlet left ventricle).

**Semilunar valves**

The semilunar or arterial valves are the connecting structures between the ventricular masses and great arteries. The valvular components usually described during an anatomic evaluation include the annulus, cusps, commissures, sinuses, sinotubular junction, and supporting ventricular musculature. Other important elements to assess as part of the examination include valvular patency, degree of hypoplasia (when present), and potentially related abnormalities.

**Figure 4.33 Types of conus (infundibulum).** The location of the muscular infundibulum categorizes the conal anatomy into four basic types: subpulmonary conus, as found in the normal heart; subaortic conus, as often found in transposition of the great arteries; bilateral conus (in subpulmonary and aortic locations), as usually identified in patients with double-outlet right ventricle; and bilaterally absent (rare), as may be found in some patients with double-outlet left ventricle. (Source: Geva [105]. Reproduced with permission of Wiley.)

**Ventriculoarterial connections**

To determine the type of VA connection, one must examine the outflow tracts to define the ventricular origin of the great arteries and the relationship between the semilunar valves and the ventricles. There are no intrinsic features that distinguish between the great arteries, and therefore the branching pattern of the arterial trunks is used to establish their identity (see the sections that follow) [147]. Four basic VA connections are recognized: concordant, discordant, double-outlet, and single-outlet.

In **VA concordance** (connection to an appropriate ventricle), the pulmonary artery arises from the right ventricle and the aorta arises from the left ventricle. This connection has been considered normal in solitus normal or inverted normal. This relationship is in contrast to a **discordant VA connection** (connection to an inappropriate ventricle), in which the pulmonary artery arises from the left ventricle and the aorta arises from the right ventricle, as is most commonly seen in transposition of the great arteries (e.g., D-transposition, L-transposition, or A-transposition). Other connection types include double outlet and single outlet, as shown in Figure 4.34. The term **double outlet** is used when both great arteries originate from one ventricle.
or when one vessel arises from the ventricle and the second overrides the septum by over 50% (e.g., double-outlet right ventricle). Another criterion used to identify this type of connection is a lack of fibrous continuity between the mitral valve and adjacent semilunar valve. A single-outlet connection refers to a solitary great artery arising from the ventricle, the other being atretic (e.g., pulmonary atresia and aortic atresia) or a common arterial trunk (e.g., truncus arteriosus).

**KEY POINTS: VENTRICULOARTERIAL JUNCTION**

- A muscular infundibulum (conus) normally separates the tricuspid and pulmonary valves, in contrast to the presence of fibrous continuity between the mitral and aortic valves.
- Examination of the semilunar valves is an important aspect of CHD evaluation.
- Determination of the type of VA connection requires definition of the ventricular origin of the great arteries and the relationship between the semilunar valves and the ventricles.
- No intrinsic feature distinguishes between the great arteries, and therefore the branching pattern of the arterial trunks is used to establish their identity.
- The four basic VA connections are concordant, discordant, double outlet, and single outlet.

**Great arteries and their relationships**

As described in detail earlier in this chapter, the developmental changes that occur in the conotruncal region during embryonic life result in a spiral or criss-cross relationship between the great arteries in the normal heart. In individuals with normally related great arteries, the main pulmonary artery is anterior to the aorta and courses leftwards before bifurcating into the left and right branches,
whereas the aorta is posterior with respect to the main pulmonary artery and courses rightwards, giving rise to the coronary arteries, the vessels of the head and neck, and most systemic arteries. In addition, the pulmonary valve sits anterior to and leftwards of the aortic valve. This great artery/semilunar valve relationship may be altered, resulting in a parallel (i.e., side-by-side) relationship and other abnormal spatial orientations. As part of a complete examination, the spatial relations between the great arteries and the semilunar valves (anterior-posterior and right–left position) should be described. The Van Praagh system [174] defines the types of great arterial situs (i.e., spatial relations of the great arteries) as follows:

- **solitus** (aortic valve right-sided relative to pulmonary valve) – normally related great arteries (S), or D-transposition/malposition (D)
- **inversus** (aortic valve left-sided relative to the pulmonary valve) – inverted (mirror image), normally related great arteries (I), or L-transposition/malposition (L)
- **ambiguous** (right-left location of the aortic valve, directly anterior to the pulmonary valve, is equivocal, meaning neither right or left) – A-transposition/malposition (A).

**KEY POINTS: GREAT ARTERIES AND THEIR RELATIONSHIPS**

- An important component of the morphologic examination in CHD is the description of the spatial relationships between the great arteries and the semilunar valves.
- In the normal heart, there is a spiral or criss-cross relationship between the great arteries; this relationship may be altered, resulting in a parallel relationship and other abnormal spatial orientations.
- The great arterial situs in the Van Praagh system is defined as solitus, inversus, or ambiguous.

**Branch pulmonary arteries and ductus arteriosus**

In the normal heart, the main pulmonary artery emerges from the morphologic right ventricle and courses to the left of the ascending aorta. The main pulmonary artery bifurcates into right and left branches. The course of each branch is distinct: the right pulmonary artery originates almost in perpendicular fashion from the main pulmonary artery and travels beneath the aortic arch and posterior to the SVC, whereas the left pulmonary artery continues in a smooth arch-like fashion from the pulmonary confluence over the left mainstem bronchus. As indicated previously, the thoracic organs are asymmetrical, which accounts for the different branching patterns of the right and left pulmonary arteries and their relationships to the tracheobronchial tree. These differences facilitate the determination of lung morphology and sidedness.

The ductus arteriosus is a vascular channel that serves as an essential communication between the pulmonary artery and the descending aorta during fetal life. In most cases, the ductus arteriosus originates from the postero-superior aspect of the junction between the main and left pulmonary arteries and inserts into the anterolateral or ventral aspect of the descending thoracic aorta, just distal to the left subclavian artery. However, the site of origin and the course of the ductus arteriosus can be variable, which is most likely to be the case in complex cardiac pathology. This channel should spontaneously close soon after birth. If it fails to close, a persistent connection between the great arteries is created, which allows for shunting (i.e., PDA). In certain types of congenital malformations, patency of this communication is essential for either pulmonary or systemic blood flow and, therefore, for survival.

**Aortic arch**

The aortic arch can be divided into three components: the ascending, transverse, and descending portions. The origin of the three arch vessels (brachiocephalic, carotid, and subclavian arteries) should be determined as part of the aortic arch evaluation. An examination of these structures should focus on assessing vessel patency and size, aortic arch position, aortic arch sidedness, and branching pattern (i.e., origin of the head and neck vessels). Vascular anomalies or variants should also be identified. Aortic arch sidedness is defined by which bronchus is crossed by the aortic arch or, likewise, by the position of the aortic arch relative to the trachea. The aortic arch is normally left-sided, and the aortic arch vessels branch in sequence into the right innominate (which divides into the right subclavian and right carotid arteries), left carotid, and left subclavian arteries.

**KEY POINTS: BRANCH PULMONARY ARTERIES, DUCTUS ARTERIOSUS, AND AORTIC ARCH**

- The main pulmonary artery arises anteriorly from the morphologic right ventricle and courses to the left of the ascending aorta bifurcating into its right and left branches
- The ductus arteriosus is an essential communication between the great arteries during fetal life. It usually originates at the junction between the main and left pulmonary arteries and inserts into the ventral aspect of the descending thoracic aorta, just distal to the left subclavian artery.
- Important aspects of the aortic arch examination include determination of sidedness (normally left-sided) and branching pattern.
- Vascular anomalies or variants are also characterized.

**Coronary arteries**

An examination of the major epicardial coronary arteries, including their origin, proximal course, and branching
pattern, is another essential component of the anatomic evaluation for CHD. Normally, two coronary arteries (the right and left main) arise from the aortic root from their respective sinuses of Valsalva facing the main pulmonary artery. The left main coronary artery bifurcates into the left anterior descending and circumflex coronary arteries. In the clinical setting, advanced imaging modalities are required to assess the more distal branches of the main vessels (e.g., diagonals, marginals, and septal perforators) and the dominant coronary system (determined by the origin of the posterior descending branch). The right and circumflex coronary arteries normally course along the AV groove and near the AV valves. The left anterior descending coronary artery travels along the interventricular septum. Variations from these patterns or abnormalities in the origin, course, or branching of the coronary arteries may be recognized clinically as incidental findings, and they may be found in isolation or in association with other cardiac defects.

**Description of associated malformations**

In addition to the detailed examination described in previous sections, any morphologic approach for evaluating the cardiovascular system and major cardiac defects requires an accurate and detailed assessment of any co-existing malformations as part of a comprehensive anatomic analysis for CHD.

**Summary – nomenclature for CHD**

Caring for patients with structural malformations of the cardiovascular system is an important aspect of anesthesia practice and the main focus for those who specialize in the management of patients with CHD. The spectrum of these malformations ranges widely from relatively simple defects to complex ones. To provide optimal care for patients with CHD, one must have a solid understanding of the anatomic abnormalities, the altered pathophysiology, and the associated hemodynamic consequences of the disease. Important requirements in this regard include having a solid framework concerning the steps involved in the morphologic evaluation of the heart as described in this section of the chapter and summarized in Figure 4.35, the nomenclature used to refer to these anomalies, and the terminology that identifies the anatomic alterations.

**Selected References**

A full reference list for this chapter is available at:
http://www.wiley.com/go/andropoulos/congenitalheart

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Introduction

The circulatory system in congenital heart disease (CHD) continually changes and develops in response to both normal and pathologic stimuli. The response to anesthetic and surgical interventions must be understood in this framework, and is often radically different from the usual, expected pediatric and adult situations with a “normal” cardiovascular system. This chapter will review developmental changes of the cardiovascular system from fetal life through to adulthood, in both the normal and pathophysiologic states associated with CHD. Not much is known about the development of the normal and diseased human heart. Much of the information discussed in this chapter was derived from animal models, and new information will undoubtedly be discovered as human myocardial tissue is studied.

Development from fetus to neonate

Circulatory pathways

The fetus receives oxygenated and nutrient-rich blood from the placenta via the umbilical vein, and ejects desaturated blood through the umbilical arteries to the placenta; thus the placenta, not the lung, serves as the organ of respiration. Blood flow largely bypasses the lungs in utero, accounting for only about 7% of the fetal combined ventricular output [1]. Pulmonary vascular resistance (PVR) is high, and the lungs are collapsed and filled with amniotic fluid. This is the basis for the fetal circulation, which is a parallel circulation, rather than the series circulation seen postnatally. Three fetal circulatory shunts exist to carry better-oxygenated blood from the umbilical vein to the systemic circulation: the ductus venosus, ductus arteriosus, and foramen ovale (Figure 5.1A) [2].
Approximately 50% of the umbilical venous blood, with an oxygen tension of about 30–35 mmHg, passes through the ductus venosus, and then into the right atrium. There it streams preferentially across the foramen ovale, guided by the valves of the sinus venosus and Chiari network into the left atrium. Thus the brain and upper body preferentially receive this relatively well-oxygenated blood, which accounts for 20–30% of the combined ventricular output. Blood returning in the inferior vena cava represents about 70% of the total venous return to the heart, and two-thirds of this deoxygenated blood passes into the right atrium and ventricle. About 90% of the blood flows through the ductus arteriosus to supply the lower fetal body.

After birth, there is a dramatic fall in PVR and increase in pulmonary blood flow, with inflation and oxygenation of the lungs (Figure 5.2) [3]. The placental circulation is removed, and all of these changes lead to closure of the ductus venosus, constriction of the ductus arteriosus, and reversal of pressure gradients in the left and right atria, leading to closure of the foramen ovale. This leads to a state called the transitional circulation (Figure 5.1B), characterized by high pulmonary artery pressures and resistance (much lower than in utero, however), and a small amount of left-to-right flow through the ductus arteriosus. This is a labile state, and failure to maintain lower PVR can rapidly lead to reversion to fetal circulatory pathways, and right-to-left shunting at the ductus arteriosus and foramen ovale. This maintenance of fetal circulatory pathways is necessary for survival in many CHDs, particularly those dependent on a patent ductus arteriosus for all or a significant portion of systemic or pulmonary blood flow, or atresia of atrioventricular valves. Maintenance of ductal patency with prostaglandin E1 (PGE1) is crucial in these lesions. In a two-ventricle heart with large intracardiac shunts, maintenance of the fetal circulation leads to right-to-left shunting at the foramen and ductal levels, and thus hypoxia. Conversion to the mature circulation (Figure 5.1C) in the normal heart occurs over a period of several weeks, as the PVR falls further, and the ductus arteriosus closes permanently by thrombosis, intimal proliferation, and fibrosis. Factors favoring the transition from fetal to mature circulation include normal oxygen tensions and physical expansion of the lungs, normal pH, nitric oxide, and prostacyclin. Factors favoring reversion to
fetal circulation include low oxygen tension, acidotic pH, lung collapse, and inflammatory mediators (leukotrienes, thromboxane A2, platelet-activating factor) as seen in sepsis and other related conditions, and endothelin A receptor activators [4].

Myocardial contractility

The fetal myocardium is characterized by poorly organized cellular arrangements, and fewer myofibrils with a random orientation, in contrast to the parallel, well-organized myofibrillar arrangement of the adult myocardium [5] (see later in this chapter). Fetal hearts develop less tension per gram than adult hearts, because of increased water content and fewer contractile elements. Calcium cycling and excitation contraction coupling are also very different, with poorly organized T-tubules and immature sarcoplasmic reticulum, leading to more dependence on free cytosolic ionized calcium for normal contractility. Despite this immature state, the fetal heart can increase its stroke volume in a limited fashion up to left atrial pressures of 10–12 mmHg according to the Frank–Starling relationship, as long as afterload (i.e., arterial pressure) is kept low [6]. These features continue throughout the neonatal and early infancy period.

KEY POINTS: DEVELOPMENT FROM FETUS TO NEONATE

- The transition from fetus to neonate involves a decrease in PVR, elevation of left heart pressures, and closure of shunts at the ductus arteriosus, foramen ovale, and ductus venosus.
- The transitional circulation is an intermediate state between fetal and adult circulation and may revert to fetal circulation with persistence of hypoxemia, acidosis, or CHD, or other conditions with elevated pulmonary artery pressures.
- The fetal heart develops less tension per gram of resistance than the mature heart and has limited ability to increase stroke volume up to left atrial pressure of only 10–12 mmHg.

Development from neonate to older infant and child

At birth, the neonatal heart must suddenly change from a parallel circulation to a series circulation, and the left ventricle in particular must adapt immediately to dramatically increased preload from blood returning from the lungs, and increased afterload as the placental circulation is removed. The very high oxygen consumption of the newborn necessitates a high cardiac output for the first few months of life. However, animal models have demonstrated that the fetal and newborn myocardium develops less tension in response to increasing preload (sarcomere length), and that cardiac output increases less for the same degree of volume loading [7,8] (Figure 5.3). Resting tension, however, is greater in the newborn than in the mature heart. This information suggests that the newborn heart is operating near the top of its Frank–Starling curve, and that there is less reserve in response to both increased afterload and preload. This observation is borne out clinically in newborns after complex heart surgery, who are often intolerant of even small increases in left atrial pressure or mean arterial pressure. The newborn myocardium also has only a limited ability to increase its inotropic state in response to exogenous catecholamines, and is much more dependent on heart rate to maintain cardiac output than is the mature heart. One reason for this is the high levels of circulating endogenous catecholamines that appear after birth, necessary to make the transition to extrauterine life [9]. As these levels decrease in the weeks after birth, contractile reserve increases.

The neonatal myocardium is less compliant than the mature myocardium, with increased resting tension as noted earlier, and a significantly greater increase in ventricular pressure with volume loading [10]. This implies that diastolic function of the neonatal heart is also impaired compared with the mature heart [11]. The myofibrils of the newborn heart also appear to have a greater sensitivity to calcium, developing a greater tension than adult myofibrils when exposed to the same free Ca\(^{2+}\) concentration in vitro [12].

It must again be emphasized that nearly all of this data was obtained from animal models, and although the information appears to agree with what is observed clinically, there is a need for non-invasive studies of normal human hearts from the neonatal period through adulthood to confirm these impressions of cardiac development.

Gene expression in cardiac development

Recent progress has been made in understanding the genetic aspects of human cardiac development, and in contrast to the physiologic studies which are almost exclusively performed in animal models, small amounts of human cardiac tissue obtained from biopsy or autopsy specimens can be used for these studies. Some aspects of these developmental changes will be reviewed.

Myosin is the major protein component of the thick filaments of the cardiac myofibril, and differences in the expression of this protein may play a significant role in myocardial contractility. Chromosome 14 has the genetic material responsible for producing the myosin heavy chain which makes up the backbone of the thick filaments, and two major isoforms, \(\alpha\) and \(\beta\), exist. The \(\beta\) isoform predominates, and does not change significantly with maturation [13]. The myosin light chain has multiple isoforms, and the relative proportions of these isoforms changes with development, and also in response to pressure loading of the heart. The isoforms that predominate in the newborn myocardium appear to confer a greater
sensitivity to Ca\(^{2+}\) than those seen in the mature heart [14] and may contribute to the increased sensitivity of the neonatal myocardium to Ca\(^{2+}\).

Troponin I, C, and T are critical proteins that bind Ca\(^{2+}\) and regulate the interaction between myosin and actin, directly affecting the force of contraction. Troponin C, the Ca\(^{2+}\)-binding portion of the troponin moiety, does not change with development. Troponin I, however, has two major isoforms, a slow skeletal muscle type that predominates in the heart in fetal and neonatal life, and the cardiac isoform, which is the only isoform expressed in the mature heart [15]. Only the cardiac (mature) isoform responds to ß-adrenergic stimulation, producing a faster twitch development and greater twitch tension. However, contractility in the neonatal myofibrils containing the immature myosin light chain isoform are more resistant to acidosis. Four isoforms of troponin T are expressed in the fetal and neonatal heart, but only one in the mature heart. These isoforms exhibit different levels of ATPase activity and Ca\(^{2+}\) sensitivity (see later), with greater ATPase activity and Ca\(^{2+}\) sensitivity seen in the immature forms [12]. Tropomyosin [16] has two isoforms and actin [17] has three, which are expressed in different proportions as developmental changes occur, but the functional significance of these changes has yet to be elucidated.

Some enzymes are affected by the loading conditions of the heart. Protein kinase C (PKC) is an enzyme with a major role in transmembrane signal transduction through phosphorylation of a number of downstream intracellular components (see the section on “Calcium cycling in the normal heart”) [18]. There are six isoforms of this enzyme, and it is not affected during development. However, in aortic stenosis producing left ventricular hypertrophy, all isoforms except PKC-β are dramatically upregulated, and in dilated cardiomyopathy there is a dramatic upregulation of PKC-β. Phosphodiesterase (PDE) is an enzyme involved in the termination of the action of cyclic adenosine monophosphate (cAMP), which regulates the contractile state of the myocardium (see later). Expression of the isoform PDE-5 is dramatically increased in the hypertrophied human right ventricle in patients with pulmonary hypertension, and inhibition of this enzyme improves ventricular contractility [19].

New information is available about the molecular and cellular basis for normal cardiac development and the causes of CHD [20]. A missense mutation in the myocardial protein actin has been discovered to be the cause of isolated secundum atrial septal defect in some patients [21]. Pluripotent cardiac progenitor cells reside in the human neonatal myocardium in relatively high numbers during the first month of life [22]. This knowledge has given rise to the exciting notion that these stem cells could potentially be used to facilitate recovery from cardiac morbidity or to enhance surgical repair.

**The extracellular matrix**

The extracellular matrix of the heart is important in translating the force generated from shortening of sarcomere length to the cardiac chambers, resulting in stroke volume.
The major components of the extracellular matrix are collagen types I and II, glycoproteins, and proteoglycans and the expression of these elements changes with development. The neonatal heart has a higher content of both total and type I collagen (which is stiffer and less compliant than type III collagen) when compared with the total protein content of the heart [23]. The collagen to total protein ratio reaches mature levels by about 5 months of life. This change, along with greater water content of the immature myocardium, may partially explain the diminished diastolic function. Also this relative lack of contractile elements reduces the ability of the neonatal myocardium to increase its inotropic state. A network of collagen-based connections, called the weave network, develops rapidly after birth, connecting myocytes and capillaries and allowing greater functional integrity to develop in response to the greater afterload stress on the heart [24]. This development of the extracellular matrix appears to be complete by approximately 6 months of age, and results in a much more efficient transfer of force generated by sarcomere shortening to the cardiac chambers (Figure 5.4) [12].

The connection of the cardiac myocyte to the extracellular matrix is maintained by two specialized complexes that together comprise over 20 proteins, the costameres, and the dystrophin-associated glycoprotein complexes [25,26] (Figure 5.5). The costameres produce a physical connection between the sarcomeres at the Z disk and the extracellular matrix. Transmembrane proteins called integrins connect the sarcolemma to the extracellular matrix. Integrins are receptors which are specific for collagen and fibronectin, and cause the attachment of the extracellular matrix to the myocytes, allowing force transduction to occur [27]. Collagen and vinculin, another cytoskeletal protein, are attached to the sarcomere at the Z disk. The integrins have two subunits, α and β, which express several isoforms, the relative proportions of which change during development to those that afford greater adherence of the cytoskeletal proteins to the myocytes, resulting in greater structural integrity.

Dystrophin-associated glycoprotein complexes also contribute to a substantial mechanical linkage from the extracellular matrix to the cardiac cytoskeleton, and contribute to force transduction [25,26]. The proteins dystrophin, sarcoglycans, dystroglycan, and dystrobrevins are included in these complexes. These complexes play an integral role in cardiac function, and mutations in these proteins can be associated with cardiomyopathies, especially the muscular dystrophy-associated cardiomyopathies. Reduction of dystrophin activity results in dilatation of all four cardiac chambers and reduced ventricular function. Mutations in dystrobrevins have been associated with left ventricular non-compaction.

Cell-to-cell connectivity
The intercalated discs mediate the cell-to-cell interactions that coordinate cardiac myocyte activity resulting in synchronous contraction, and maintaining the structural integrity of cardiac tissue [28] (Figure 5.6). These discs are situated in between cardiac myocytes at the longitudinal ends of the cells and consist of three types of connections: desmosomes, fascia adherens junctions, and gap junctions. The desmosomes have both intracellular and intercellular components. This structure serves to integrate signals from both cell-to-matrix and cell-to-cell interactions, ensuring force transmission, cell membrane integrity, and biochemical signaling. The fascia adherens junctions are responsible for holding the cardiac myocytes tightly together, and they anchor myofibrils and ensure transmission of contractile forces from cell to cell. Finally, the gap junctions form the electrical coupling apparatus between individual myocytes, ensuring rapid propagation of the electrical impulse, forming an electrical syncytium and thus triggering the coordinated contraction of cardiac myocytes. Mutations in intercalated disc proteins have recently been found to be associated with cardiac disorders. These include adherens junctions mutations associated with heart failure and dilated cardiomyopathy, and desmosome complex mutations associated with some forms of arrhythmogenic right ventricular cardiomyopathy.

The preceding short review is meant to give the reader an idea of some of the aspects of the cellular biology of the
developing circulation. The explosion of new information in this area, and especially new data from human tissue, will lead to a more thorough understanding of the pathophysiology of disease states and suggest avenues for future treatment. For a more complete treatment of this area, the reader is referred to several excellent reviews [29–31].

**Innervation of the heart**

Clinical observations in newborn infants have led to the hypothesis that the sympathetic innervation and control of the cardiovascular system are incomplete in the newborn infant compared with older children and adults, and that the parasympathetic innervation is intact [5]. Examples of this include the frequency of bradycardia in the newborn in response to a number of stimuli, including vagal and vagotonic agents, and the relative lack of sensitivity in the newborn to sympathomimetic agents. Histologic studies in animal models have demonstrated incomplete sympathetic innervation in the neonatal heart when compared with the adult, but no differences in the number or density of parasympathetic nerves [32,33].

Autonomic cardiovascular control of cardiac activity can be evaluated by measuring heart rate variability in response to both respiration and beat-to-beat variability in systolic blood pressure [34]. The sympathetic and parasympathetic inputs into sinoatrial node activity contribute to heart rate variability changes, with greater heart rate variability resulting from greater parasympathetic input into sinoatrial node activity [35]. Studies using these methodologies for normal infants during sleep suggest that the parasympathetic predominance gradually diminishes until approximately 6 months of age, coinciding with greater sympathetic innervation of the heart similar to adult levels [36].

**KEY POINTS: DEVELOPMENT FROM NEONATE TO OLDER INFANT AND CHILD**

- The neonatal heart exhibits heart rate dependence, limited ability to increase contractile state, and limited tolerance for excessive afterload and preload.
The costameres and dystrophin-associated glycoprotein complexes play central roles in connection of the cardiac myocyte to the extracellular matrix and thus force transduction in the heart.

- The intercalated discs maintain cell-to-cell connectivity between cardiac myocytes, allowing tight adhesion and electrical impulse transition to facilitate coordinated cardiac contraction.

### Development from child to adult

Beyond the transition period from fetal to newborn life and into the first few months of postnatal life, there is not much human or animal information concerning the exact nature and extent of cardiac development at the cellular level. Most studies compare newborn or fetal animals with adult animals [37]. Cardiac chamber development is assumed to be influenced by blood flow [38]. Large flow or volume load in a ventricle results in ventricular enlargement. Small competent atrioventricular valves, as in tricuspid stenosis, result in lower blood flow and a small ventricle. Increases in myocardial mass with normal growth, as well as in ventricular outflow obstruction, are mainly due to hypertrophy of myocytes. Late gestational increases in blood cortisol are responsible for this growth pattern, and there is concern that antenatal glucocorticoids to induce lung maturity may inhibit cardiac myocyte proliferation. In the human infant, it is assumed that the cellular elements of the cardiac myocyte (i.e., adrenergic receptors, intracellular receptors and signaling, calcium cycling and regulation, and interaction of the contractile proteins) are similar to those of the adult by approximately 6 months of age. Similarly, cardiac depression by volatile anesthetic agents is greater in the newborn, changing to adult levels by approximately 6 months of age [39].

### Normal values for physiologic variables by age

It is useful for the anesthesiologist to be aware of normal ranges for physiologic variables in premature and full-term newborns of all sizes, and in infants and children of all ages (Table 5.1, Figure 5.7) [40]. Obviously, acceptable ranges for these variables are highly dependent on the individual patient’s pathophysiology, but the wide range of “normal” values may reassure the practitioner to accept “low” blood pressure, for example, if other indices of cardiac function and tissue oxygen delivery are acceptable. Values for awake, healthy infants and children are often significantly different than in anesthetized patients and those with significant cardiac disease undergoing invasive procedures, especially with regard to the higher resting blood pressure values [41–43].

### Myocardial sequelae of longstanding CHD

Hypertrophy of the cardiac chambers is a common response to a number of different chronic pathophysiologic states. Wall thickness increases though hypertrophy of the cardiac myocytes and non-contractile elements.
Table 5.1 Normal heart rates and systolic blood pressure as a function of age.

<table>
<thead>
<tr>
<th>Age</th>
<th>Range of normal heart rates (beats/minute)</th>
<th>Range of normal systolic blood pressures, measured by oscillometric blood pressure device (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonate (&lt;30 days)</td>
<td>120–160</td>
<td>60–75</td>
</tr>
<tr>
<td>1–6 months</td>
<td>110–140</td>
<td>65–85</td>
</tr>
<tr>
<td>6–12 months</td>
<td>100–140</td>
<td>70–90</td>
</tr>
<tr>
<td>1–2 years</td>
<td>90–130</td>
<td>75–95</td>
</tr>
<tr>
<td>3–5 years</td>
<td>80–120</td>
<td>80–100</td>
</tr>
<tr>
<td>6–8 years</td>
<td>75–115</td>
<td>85–105</td>
</tr>
<tr>
<td>9–12 years</td>
<td>70–110</td>
<td>90–115</td>
</tr>
<tr>
<td>13–16 years</td>
<td>60–110</td>
<td>95–120</td>
</tr>
<tr>
<td>&gt;16 years</td>
<td>60–100</td>
<td>100–125</td>
</tr>
</tbody>
</table>

Blood pressure data are from references [40–43].

The hypertrophy reduces wall stress in the dilated heart, but also serves to reduce ventricular function, particularly diastolic function. This reduction in function serves to reduce myocardial oxygen consumption in response to a wide variety of chronic stresses, in both pressure and volume overloaded ventricles [44].

Pressure overload hypertrophy results in altered gene expression in the cardiomyocyte. Myosin isoform expression (see later) changes from the faster-reacting α-myosin to the slower β-myosin, reducing myocardial function [45].

Integrin-linked kinase expression is increased in patients with hypertrophic cardiomyopathy and induces hypertrophy in an animal model [46]. Altered expression or mutations of other genes that regulate production of cardiac cytoskeletal proteins, such as dystrophin, occur in patients with end-stage cardiomyopathy [47,48].

Cardiomyocyte receptor function in normal and diseased hearts

The adrenergic receptor

The adrenergic receptors (ARs) are a part of a large superfamily of receptors that mediate their biological responses through the coupling of a specific guanine nucleotide regulatory protein, or G protein [49]. This superfamily of receptors shares a common structural motif, characterized by seven hydrophobic domains spanning the lipid bilayer. The seven domains are attached by three internal loops and three external loops between the amine terminus and the cytoplasmic carboxyl terminus. The function of this receptor family is dependent on a specific agonist (or ligand) binding to the receptor, which causes a conformational change in the receptor. This structural change permits the interaction between the intracellular portion of the receptor and the G protein. This interaction, also referred to as “coupling,” inevitably links the activated receptor to a specific biological response. The regulation of the biological response is initiated by the specificity of the receptor for a particular extracellular agonist and the coupling of a specific G protein to that activated receptor.
a series of agonists to separate the ARs into two principal receptor groups, the α and β receptor groups [51]. These findings have been confirmed repeatedly with the development of drugs that function to selectively antagonize the α receptor with no effect on the β receptor. Soon after the distinction between the α and β receptor type was known, it became more evident that the separation of α and β receptors was not sufficient to explain pharmacological studies using rank order of potency for an antagonist, differing from an agonist because it blocks the biological response. With the advent of radioligand-labeled antagonists and new molecular cloning techniques examining receptor gene expression, it became clear that the two principal receptor groups could be further subdivided into additional subtypes.

To date, within the β-adrenergic group, four different subtypes have been identified: β1, β2, β3, and β4. Pharmacologically, β1 and β2 are differentiated by their affinities to different catecholamines: epinephrine, norepinephrine, and isoproterenol. β1 has similar affinity to epinephrine and norepinephrine, while β2 has a higher affinity to epinephrine than to norepinephrine. Both β1 and β2 have the same affinity to isoproterenol. The β3 and β4 receptors have minor roles in cardiovascular function and will not be discussed further.

The expression and distribution of each subtype are highly dependent on the organ, which adds another level of specificity. Distribution of a particular receptor in two different tissue types may result in two different functions. When examining cardiovascular response to adrenergic stimulation, the β1 receptor is predominantly expressed in heart tissue. The stimulation of the receptor subtype leads to both inotropic and chronotropic effects on cardiac function, resulting in an increase in the myocardial contractile force and a shortening of contractile timing, respectively. While β2 can also be found in the heart, it is mostly expressed in vascular smooth muscle tissue. The distribution and function relevance of this receptor subtype in the heart are controversial and may change with alterations in cardiac function. The percentage of β2 receptors in the non-failing heart averages about 20% in the ventricle [52] and 30% in the atrium. The ratio of β1 to β2 receptors is approximately 75%:25% in the ventricles of younger hearts [53,54].

Each signaling pathway is specific to each adrenergic receptor. Once the agonist binds to the β1 receptor causing the coupling of the G protein, the G-protein α subunit becomes activated followed by an increase in adenylate cyclase activity, which induces the conversion of ATP to cAMP. The second messenger, cAMP, phosphorylates protein kinase A (PKA). The function of a kinase is to phosphorylate other target proteins, which initiates a biological response. PKA phosphorylates many intracellular targets, including calcium channels, troponin I, and ryanodine receptors. PKA also plays a central role in regulating calcium sensitivity [55].

The β2 receptor has also been shown to function through the cAMP signaling pathway, causing the activation of
PKA, but not nearly to the extent of β₁ in cardiomyocytes [56]. The response of this stimulation appears to have a larger effect on smooth muscle, for example the vascular smooth muscle. In this tissue type, the stimulation of β₂ and the subsequent increase in cAMP promote the vasodilation of vascular smooth muscle and may lead to alterations in blood pressure. In these tissues, the effect of β₁ stimulation appears to be minimal, due to lack of β₁ receptors in the smooth muscle.

Similar to the β receptors, the α receptors can be pharmacologically subdivided into α₁ and α₂. The α receptor is distributed in most vascular smooth muscle and, to a lesser extent, in the heart. The α₂ receptor has been found in some vascular smooth muscle; however, its major functional importance is as a presynaptic receptor in the central and peripheral nervous systems. The use of molecular techniques has identified three additional subtypes of the α₁ receptor (α₁A, α₁B, and α₁D) and three additional subtypes of the α₂ receptor [49]. Binding of an agonist to an α₁ receptor in the heart or vascular smooth muscle results in activation of the G_s subunit of the G protein, which activates phospholipase C (see later), producing diacylglycerol and inositol-1,4,5-triphosphate, which releases Ca^{2+} from the sarcoplasmic reticulum and increases vascular smooth muscle tone or cardiac contractility. A schematic classification of adrenergic receptors incorporating recent knowledge of molecular pharmacology and signal transduction is presented in Figure 5.9 [49].

The adrenergic receptor concentration in cardiac tissue is very small and measured as fentomoles/mg protein. However, the response to stimulation of the receptor is greatly amplified by the signal that occurs downstream of the receptor. In rat ventricular myocytes, the ratio between the β receptors and the next two downstream signaling components (β receptor:G protein:adenylate cyclase) is 1:200:3 [57]. This demonstrates how a large response can be initiated by the activation of a small number of receptors. In addition, it also shows that the rate-limiting component that ultimately regulates intracellular production of cAMP is receptor density and the enzyme concentration of adenylate cyclase.

**Developmental changes in adrenergic receptor signaling**

Information concerning changes in adrenergic receptor function during the transition from neonatal to more mature myocardial development is limited to a few animal studies. As noted above, the neonatal heart has a limited inotropic response to catecholamine administration.

β-Adrenergic receptor density is higher in the ventricular myocardium of neonatal versus adult rabbits, but the inotropic response to the same concentration of isoproterenol is significantly greater in adult tissue [58]. In the neonatal rat, the mechanism of the β-adrenergic-mediated increase in contractility is entirely due to β₂ stimulation, whereas in the adult rat it is due solely to β₁ receptor activation. Coupling of the β₂ receptor to G_i protein action is apparently defective in the neonatal rat, because the ratio of G_i to G_s subunits is much higher in the neonate. The relative proportion of β₁ and β₂ receptors is the same in neonatal and adult hearts (83% β₁: 17% β₂), and approximates the ratio measured in children with simple acyanotic CHD, which is about 78% β₁: 22% β₂ [53].

There is animal and human evidence that α-adrenergic receptor-mediated chronotropic and inotropic effects on

![Figure 5.9](image-url)
the cardiac myocyte change with development. In the neonatal animal model, α-stimulation produces positive inotropic and chronotropic effects, whereas in the adult it produces negative effects [59,60]. The chronotropic response to α, stimulation diminished with increasing age in children being evaluated for autonomic dysfunction after vagal and sympathetic blockade [61].

**Calcium cycling in the normal heart**

Calcium assumes a central role in the process of myocardial contraction and relaxation, serving as the second messenger between depolarization of the cardiac myocyte and its contraction mediated by the actin–myosin system. Calcium’s role in this excitation–contraction coupling in the normal mature heart will be reviewed briefly before discussion of developmental changes and changes with heart failure [62].

Cardiac muscle cell contraction depends on an increase in intracellular Ca\(^{2+}\) above a certain threshold, and relaxation ensues when intracellular Ca\(^{2+}\) falls below this threshold. Two major regions of Ca\(^{2+}\) flux occur: across the sarcolemmal membrane (slow response) and release from internal stores, the sarcoplasmic reticulum (rapid release and reuptake) [63,64] (Figure 5.10). The primary site of entry of Ca\(^{2+}\) through the sarcolemmal membrane is through the L-type, or low-voltage-dependent Ca\(^{2+}\) channels, which occurs in two types, a low-threshold, rapidly inactivating channel, and a higher threshold, more slowly inactivating channel [65]. Depolarization of the sarcolemmal membrane triggers opening of these channels, resulting in the release of a large amount of Ca\(^{2+}\) from the sarcoplasmic reticulum (SR), the major internal Ca\(^{2+}\) storage organelle. Ca\(^{2+}\) entry through the slowly inactivating channels serves to fill the SR with adequate Ca\(^{2+}\) stores. Removal of Ca\(^{2+}\) from the cytoplasm to the exterior of the cell occurs via two major mechanisms: the sodium–calcium (Na\(^+\)–Ca\(^{2+}\)) exchanger, and the calcium ATPase pump. The Na\(^+\)–Ca\(^{2+}\) exchanger usually serves to exchange three sodium ions (moving into the cell) for one Ca\(^{2+}\) (moving out of the cell), although the reverse action, as well as a 1:1 exchange, are possible [66].

**Figure 5.10** Calcium cycling and its relationship to the β-adrenergic receptor system and myocyte myofilaments. See text for discussion. βAR, β-adrenergic receptor; Gs, stimulatory G protein; GRK, G-receptor kinase; cAMP, cyclic AMP; A-kinase, protein kinase A; SR, sarcoplasmic reticulum; RyR, ryanodine receptor; SERCA2, sarcoplasmic reticulum Ca\(^{2+}\)-ATPase; PLN, phospholamban; I\(_{\text{Ca,L}}\), L-type Ca\(^{2+}\) channel; FKBP, FK-506 binding protein; JP-2, junctophilin-2; GPCR, G-protein coupled receptor. Encircled P represents sites of phosphorylation by the various kinases. Numbers 1 through 7 represent targets for pharmacologic therapy in cardiac failure. (Source: Hoshijima & Chien [64]. Reproduced with permission of American Society For Clinical Investigation.)
The $\text{Ca}^{2+}$-ATPase pump actively transports $\text{Ca}^{2+}$ (in a 1:1 $\text{Ca}^{2+}$/ATP ratio) out of the cell in an energy-dependent, high-affinity but low-capacity manner [67]. The affinity of the sarcolemmal $\text{Ca}^{2+}$-ATPase pump is enhanced by calmodulin, binder of free cytoplasmic $\text{Ca}^{2+}$. Although the calcium movement through the sarcolemma plays an important role in balancing internal and external $\text{Ca}^{2+}$ concentrations and in supplying $\text{Ca}^{2+}$ to replenish SR $\text{Ca}^{2+}$ stores, and in initiating the $\text{Ca}^{2+}$-induced release of $\text{Ca}^{2+}$ from the SR, it is important to recognize that the amount of $\text{Ca}^{2+}$ flux is far less than across the SR, the far more important mechanism for excitation–contraction coupling in the mature heart [68]. The sarcolemmal $\text{Ca}^{2+}$ flux mechanisms play a much more important role in the excitation-contraction coupling of the neonatal (immature) heart.

The massive release and reuptake of $\text{Ca}^{2+}$ responsible for activation and deactivation of the actin–myosin complex and cardiocyte contraction and relaxation occurs at the level of the SR. The SR is a closed, intracellular membranous network that is intimately related to the myofilaments responsible for contraction [69,70] (Figure 5.11). The SR is connected to the sarcolemmal membrane via the transverse tubule (T-tubule) system. Depolarization of the sarcolemmal membrane results in transfer of charge down the T-tubules to the SR, resulting in the opening of SR $\text{Ca}^{2+}$ channels and the release of large amounts of $\text{Ca}^{2+}$ into the cytoplasm, where it can then bind to troponin and initiate the actin–myosin interaction. The SR is divided into longitudinal SR and terminal cisternae; the latter connect to the T-tubules. The terminal cisternae are primarily involved in the release of $\text{Ca}^{2+}$, and the longitudinal SR in its reuptake [71].

The primary $\text{Ca}^{2+}$ release mechanism of the SR is the ligand-gated $\text{Ca}^{2+}$-release channels (also known as the ryanodine receptors) that bind to the drug ryanodine. The channels are activated by two primary mechanisms: depolarization via the T-tubules, and binding of intracellular $\text{Ca}^{2+}$ itself. The predominance of one mechanism over the other differs in cardiac vs. skeletal muscle. The close proximity of the L-type sarcolemmal $\text{Ca}^{2+}$ channels in the T-tubules to the ligand-gated $\text{Ca}^{2+}$-release channels.
allows the depolarization to rapidly allow Ca\(^{2+}\) into the cell and open the SR Ca\(^{2+}\) channels. These ligand-gated Ca\(^{2+}\) release channels close when the cytosolic Ca\(^{2+}\) concentration increases; normally it opens at 0.6 μM Ca\(^{2+}\) and closes at 3.0 μM Ca\(^{2+}\).

The reuptake and sequestration of Ca\(^{2+}\) lead to relaxation of the cardiac myocyte and is an active transport mechanism, primarily involving hydrolysis of ATP by the SR Ca\(^{2+}\)-ATPase (SERCA), located in the longitudinal SR [72]. It binds two Ca\(^{2+}\) ions with high affinity and rapidly transports them to the inside of the SR. This transport system differs from the sarcolemmal membrane: it has higher affinity, allows for more rapid transport, and is not sensitive to calmodulin. Ca\(^{2+}\) is stored in the SR by calsequestrin, a high-capacity, low-affinity protein which acts as a Ca\(^{2+}\) sink.

There are two other proteins with essential roles in the regulation of Ca\(^{2+}\) flux: phospholamban and calmodulin [73,74]. Phospholamban is associated with the SERCA and can be phosphorylated by at least four different protein kinases (see earlier): cAMP-dependent, Ca\(^{2+}\)/calmodulin-dependent, cyclic guanosine monophosphate (cGMP)-dependent, or PKC. When phosphorylated, phospholamban increases the affinity of the SERCA for Ca\(^{2+}\), facilitating Ca\(^{2+}\) flux back into the SR, thus affecting the inotropic and lusitropic state of the heart. Phospholamban plays an important role in the β-adrenergic-mediated increase in inotropic state of the heart. Calmodulin is a Ca\(^{2+}\) storage protein with four binding sites, found in the cytoplasm, which interacts with the sarcolemmal Ca\(^{2+}\)-ATPase (increasing its affinity for Ca\(^{2+}\)), the SR ligand-gated Ca\(^{2+}\)-release channel (inhibits its activity at optimal cytoplasmic Ca\(^{2+}\)), and binds to the Ca\(^{2+}\)/calmodulin-dependent protein kinase [74]. Mutations in the phospholamban gene have been described, and may be a rare cause of dilated cardiomyopathy [75].

The increase in intracellular cytoplasmic Ca\(^{2+}\) initiates the contractile process. Myosin is the major component of the thick filaments, which make up the microscopic structure of the myofibril, and its interaction with actin (the major component of the thin filaments) provides the mechanical basis of cardiac muscle cell contraction [76]. Actin and myosin make up approximately 80% of the contractile apparatus, and are arranged in a parallel, longitudinal fashion, projecting from a Z-line or band (Figure 5.12) to form the basic contractile unit called the sarcomere [77]. A three-dimensional lattice consisting of interdigitated thick and thin filaments in a hexagonal array, with three thin filaments in close proximity to each thick filaments, is formed. The actin and myosin are linked by projections on the myosin protein called S1 cross-bridges, which bind to actin, and, via an energy-dependent hinge-like mechanism, produce the sliding filament cross-bridge action that is thought to produce sarcomere shortening and lengthening. The lattice is held together by connecting proteins such as titin, nebulin, and α-actinin [78]. The actin–myosin interaction is initiated when Ca\(^{2+}\) binds to troponin, a protein closely connected to actin which consists of three subunits: a Ca\(^{2+}\)-binding subunit (TNC), a tropomyosin-binding unit (TNT), and an inhibitory subunit (TNI). TNC can bind up to four Ca\(^{2+}\) ions, and this produces a conformational change on the thin filament, which allows the S1 myosin head cross-bridges to attach [79]. This also changes the TNI subunit’s conformation, and allows tropomyosin, another protein integral in filament interaction, to move aside and expose the binding sites on actin, allowing the strong binding to the S1 cross-bridges. With Ca\(^{2+}\) present, actin causes myosin ATPase to hydrolyze one

![Figure 5.12](image-url)
ATP molecule, providing energy that results in the S1 myosin head pulling on the thin filament, resulting in sarcomere shortening. Troponin C is the most important aspect of the regulation of cardiocycle contraction, and has a steep response curve to local levels of Ca\(^{2+}\). The reuptake of Ca\(^{2+}\) into the SR causes Ca\(^{2+}\) levels to rapidly decline, and the inhibitory form of the troponin, tropomyosin, actin complex returns, resulting in the reversal of the cross-bridge binding and thus sarcomere relaxation.

Besides calcium, many other regulatory mechanisms exist to influence the interaction and sensitivity of Ca\(^{2+}\) binding to troponin. These mechanisms include β-adrenergic stimulation, thyroid hormone, and phosphorylation by cAMP-dependent protein kinases.

**Developmental changes in calcium cycling**

Several aspects of the excitation–contraction system are different in the immature heart. The T-tubule is not fully formed [80], and the SR has less storage capacity and less structural organization [81], less mRNA expression [82,83], and less responsiveness to chemical blockade [84,85]. The TNI changes from a predominately cAMP-insensitive form to a cAMP-responsive form by 9 months of age, an additional factor contributing to the increased responsiveness seen with β-adrenergic stimulation after the neonatal period [85]. All of this information has led to the theory that the neonatal cardiac myocyte is more dependent than the mature heart on free cytosolic Ca\(^{2+}\) fluxes, and more susceptible to blockade of the L-type Ca\(^{2+}\) sarcolemmal channels as a mechanism of myocardial depression. The latter is thought to be the mechanism producing greater myocardial depression observed with halothane in neonatal rat models compared with sevoflurane, and the same phenomenon seen clinically [86]. A summary of the major differences in cardiac development and function between the neonatal and mature heart is presented in Table 5.2.

**Thyroid hormone**

Tri-iodothyronine (T3) has a critical role both in the development of the cardiovascular system and in acute regulation and performance. Normal T3 levels are essential for normal maturation and development of the heart through expression of genes responsible for the production of the cardiac contractile proteins, elements of the calcium cycling apparatus, and development and density of β-adrenergic receptors [87]. There are cell nucleus-mediated effects from exogenous T3 that occur from an increase in protein synthesis and require at least 8 hours to develop. These include an upregulation of β-adrenergic receptors, an increase in cardiac contractile protein synthesis, an increase in mitochondrial density, volume, and respiration, an increase in SERCA mRNA, and changes in myosin heavy chain isoforms. However, there are acute effects of T3 on cardiac myocytes that occur in minutes from interactions with specific sarcolemmal receptors, and include stimulation of L-type Ca\(^{2+}\)-pump activity, stimulation of SR Ca\(^{2+}\)-ATPase activity, increased protein kinase activity, and decrease in phospholamban [88]. Cardiac surgery and cardiopulmonary bypass interfere with the conversion of thyroxine (T4) to T3, and serum levels decrease significantly after cardiac surgery in infants and children [89]. T3 infusions improve myocardial function in children after cardiac surgery and reduce intensive care unit stay [90].

**KEY POINTS: CARDIOMYOCYTE RECEPTOR FUNCTION IN NORMAL AND DISEASED HEARTS**

- The adrenergic receptor system, particularly the β-receptor system, plays a central role in regulating cardiac contractility through G protein and adenylyl cyclase coupling.
- Calcium cycling in the neonatal heart is characterized as immature, with underdeveloped T-tubules and sarcoplasmatic reticulum, not reaching a mature state until an estimated 6–12 months of age.
- Thyroid hormone is essential for normal gene expression for production of cardiac contractile proteins, calcium cycling apparatus, and adrenergic receptor density, as well as acute effects to increase sensitivity of adrenergic receptors and efficiency of calcium cycling.

**Regulation of vascular tone in systemic and pulmonary circulations**

The regulation of vascular tone is an important consideration in the understanding and treatment of CHD. Both the systemic and pulmonary circulations have complex systems to maintain a delicate balance between vasodilating and vasoconstricting mediators in normal patients. Abnormal responses may develop that lead to pulmonary or systemic hypertension, or conversely vasodilation. A schematic representation of some of these mediators is shown in Figure 5.13 [91]. To some extent, the control mechanisms reviewed are present in both the systemic and pulmonary circulations; however, certain mechanisms are more important in one circulation. For example, the endothelial-mediated systems (nitric oxide–cGMP pathways and others) predominate in the pulmonary circulation (low-resistance circulation), whereas the phospholipase systems predominate in the systemic circulation (high-resistance circulation). The endothelium-dependent control of vascular tone plays a significant role in the transition from fetal to postnatal circulation, with pathologic persistence of fetal endothelial milieu contributing to the transitional circulation and pulmonary hypertension, both of which may influence the pathophysiology of CHD [92].
Table 5.2 Summary of major differences between neonatal and mature hearts

<table>
<thead>
<tr>
<th>Physiology</th>
<th>Neonatal</th>
<th>Mature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contractility</td>
<td>Limited</td>
<td>Normal</td>
</tr>
<tr>
<td>Heart rate dependence</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Contractile reserve</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Afterload tolerance</td>
<td>Low</td>
<td>Higher</td>
</tr>
<tr>
<td>Preload tolerance</td>
<td>Limited</td>
<td>Better</td>
</tr>
<tr>
<td>Ventricular interdependence</td>
<td>Significant</td>
<td>Less</td>
</tr>
<tr>
<td>Ca$^{2+}$ cycling</td>
<td>Sarcolemma</td>
<td>SR</td>
</tr>
<tr>
<td>Predominant site of Ca$^{2+}$ flux</td>
<td></td>
<td>Lower</td>
</tr>
<tr>
<td>Dependence on normal Ca$^{2+}$</td>
<td>High</td>
<td>Lower</td>
</tr>
<tr>
<td>Circulating catecholamines</td>
<td>High</td>
<td>Normal</td>
</tr>
<tr>
<td>Adrenergic receptors</td>
<td>Down-regulated, insensitive</td>
<td>β$_1$ predominant</td>
</tr>
<tr>
<td>β$_2$, α$_1$ predominant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Innervation</td>
<td>Parasympathetic predominates; sympathetic incomplete</td>
<td>Complete</td>
</tr>
<tr>
<td>Cytoskeleton</td>
<td>High collagen and water content</td>
<td>Lower collagen and water content</td>
</tr>
<tr>
<td>Cellular elements</td>
<td>Incomplete SR, disorganized myofibrils</td>
<td>Mature SR, organized myofibrils</td>
</tr>
</tbody>
</table>

SR, sarcoplasmic reticulum.

Pulmonary circulation

Vasoactive metabolites of arachidonic acid, called eicosanoids, are produced in cell membranes. Eicosanoids metabolized via the lipoxygenase pathway will form leukotrienes, and those metabolized via the cyclooxygenase pathway form the prostaglandins. Important vasodilating prostaglandins include PGE$_1$, which also promotes and maintains patency of the ductus arteriosus. Prostacyclin, PGI$_2$, is a potent pulmonary vasodilator [93]. Prostaglandins act in vascular smooth muscle of the systemic and pulmonary circulations by binding to receptors in the smooth muscle cell membrane, activating adenylate cyclase and increasing cAMP concentrations, which lead to lower Ca$^{2+}$ levels and a reduction of vascular tone. Thromboxane A2 is a potent leukotriene that has the opposite effects of the prostaglandins, producing vasoconstriction and platelet aggregation. Imbalance in this system caused by chronic hypoxia can lead to chronic pulmonary hypertension [94,95].

Nitric oxide (NO) is an endothelium-derived relaxant factor that causes relaxation of vascular smooth muscle cells after diffusing into the cell and activating guanylate cyclase, increasing the concentration of cGMP, leading to a reduction in the local concentration of Ca$^{2+}$ and thus reducing vascular tone [96]. Calcium-sensitive potassium channels contribute to the vasodilatation caused by NO via a cGMP-dependent protein kinase [97]. NO is formed from L-arginine by NO synthase, and is almost immediately inactivated by binding to hemoglobin. Phosphodiesterase V breaks down cGMP, so the phosphodiesterase-inhibiting drugs, such as sildenafil, potentiate NO-mediated vasodilatation [98].

Endothelins are powerful endothelium-derived vasoactive peptides, and endothelin-1 (ET-1) is the one that is best characterized. ET-1 is produced from proendothelin-1 by endothelin-converting enzymes in the endothelial cells of systemic and pulmonary vasculature. Increased pressure, shear stress, and hypoxia can lead to increased production of ET-1 in the pulmonary circulation. Two ET-1 receptors, ETA and ETB, mediate effects on smooth muscle vascular tone [99]. The ETA receptor is found on the smooth muscle cell membrane and mediates vasoconstriction, while the ETB receptor is located on the endothelial cell itself, and results in increased NO synthase activity, producing vasodilation. The primary activity of ET-1 appears to be to stimulate the ETA receptor, and indeed increased levels of ET-1 are found in many pulmonary hypertensive states such as Eisenmenger syndrome and primary pulmonary hypertension [100]. ET-1 increases in response to shear stress, hypoxia, or ischemia, and results in elevated intracellular Ca$^{2+}$ and increased sensitivity to Ca$^{2+}$, increasing pulmonary vascular tone and pressure [95].

Systemic circulation

There are multiple levels of control over the peripheral circulation. Neural control by the sympathetic and parasympathetic nervous systems is produced from stimulation of receptors on the afferent limb such as stretch receptors within the walls of the heart, and baroreceptors in the walls of arteries, such as the aortic arch and carotid sinuses. Stretch in the arterial wall stimulates the baroreceptors, producing vasodilation and heart rate slowing mediated by the vasomotor centers of the medulla [101]. Atrial stretch receptors inhibit secretion of vasopressin from the hypothalamus. The efferent limb of the autonomic nervous system consists of sympathetic and parasympathetic nerve fibers. The sympathetic nerves can be divided into vasoconstrictor...
Figure 5.13 Schematic of some major mediators of vascular tone in the pulmonary circulation. ET, endothelin-1; PROET, proendothelin-1; ECE, endothelin-converting enzyme. See text for explanation. (Source: Haynes & Webb [91]. Reproduced with permission of The Biochemical Society and the Medical Research Society.)
and vasodilator fibers. When stimulated, the vasoconstric-
tor fibers release norepinephrine, activating α-adrenergic
receptors and producing vasoconstriction. The vasodia-
tor fibers release acetylcholine or epinephrine, and
are mainly present in skeletal muscle. Parasympathetic
fibers are vital in control of heart rate and function, but
have only a minor role in controlling the peripheral
circulation [102].

Hormonal control and receptor-mediated intra-
cellular signaling are other important mechanisms.
Norepinephrine primarily stimulates peripheral α recep-
tors and causes vasoconstriction. It is secreted by the
adrenal medulla and by sympathetic nerves in proximity
to the systemic blood vessels. Epinephrine is also secreted
by the adrenal medulla, but its primary action is to
stimulate the β2 receptors in the peripheral circulation,
causing vasodilation through cAMP-mediated reductions
in intracellular Ca2+ concentrations.

Angiotensin II is produced by activation of the
renin–angiotensin–aldosterone axis in response to
reduced flow and pressure sensed by the juxtaglomerular
apparatus in the kidney. Renin produces angiotensin I
by cleaving angiotensinogen, and angiotensin II is pro-
duced when angiotensin I passes through the lung by
angiotensin-converting enzyme. Angiotensin II is a potent
vasoconstrictor, and also induces the hypothalamus to
secrete vasopressin (antidiuretic hormone), which also has
vasoconstrictor properties.

Atrial natriuretic factor (ANF) is released from atrial
myocytes in response to stretch (elevation of right or left
atrial pressure) on the atrium. ANF has vasodilatory and
cardioinhibitory effects, and causes sodium retention from
decreased tubular reabsorption of sodium in the kidney
[103]. B-type natriuretic peptide (BNP) is released by
ventricular myocardium, also in response to stretch, and
causes an increase in cGMP, leading to vasodilatation in
both arterial and venous systems. In addition, it increases
urinary sodium and water excretion [104].

Second messenger systems affect the activation of
receptors on systemic vascular cell membranes, leading to
changes in vascular tone. The phosphoinositide signaling
system is the common pathway for many of these agonists
[101] (Figure 5.14). Membrane kinases phosphorylate
phosphatidylinositol, which is an inositol lipid located
mainly in the inner lamella of the plasma membrane,
producing phosphatidylinositol 4,5 biphosphate. The
second messenger, inositol 1,4,5-triphosphate, is pro-
duced from this compound by the action of the enzyme
phospholipase C (PLC) [105]. The sequence begins with the
binding of an agonist, such as angiotensin II, vasopressin,
norepinephrine, or endothelin, to a receptor with seven
membrane-spanning domains. This receptor is linked to
activated Gq protein subunit, which in turn stimulates
phosphatidylinositol-specific PLC (PI-PLC) to produce
inositol 1,4,5-triphosphate, which acts to cause release of
Ca2+ from the SR, activating the actin–myosin system
in the smooth muscle cells, producing vasoconstriction.

Another second messenger, 1,2-diacylglycerol, is also pro-
duced, which goes on to activate protein kinase C, which
in turn has a role in mitogenesis and thus proliferation of
smooth muscle cells. There are many isozymes of PLC;
the form implicated in this series of events is the PLCγ
form. The PLCγ isoform is activated when cell growth
factors such as platelet-derived growth factor bind to
their receptors on the cell surface and active tyrosine
kinases. This results in the production of phosphatidyl-
inositol 3,4,5-triphosphate, which is also implicated in
mitogenesis.

Vasodilatation of the systemic circulation results from
the formation of nitric oxide by nitrovasodilators, or by
activation of β2-adrenergic receptors in the peripheral
vasculature, both of which result in the activation of
guanylate cyclase and the production of cGMP, which
reduces intracellular Ca2+ concentrations, producing
vasodilatation [106].

The vascular beds in various peripheral tissues differ in
the amount of local metabolic control of vascular tone. For
example, pH has much more influence on the pulmonary
circuit, with low pH leading to vasoconstriction and higher
pH leading to vasodilatation, than in the vascular tone
of other tissues. Local CO2 concentration is much more
important to central nervous system vasculature, with
high levels leading to vasodilatation. Decrease in oxygen
tension will often lead to vasodilatation, as adenosine is
released in response to the decreased oxygen delivery;
however, decreased oxygen tension increases tone in the
pulmonary circulation. Autoregulation, or maintaining
relatively constant blood flow over a wide range arterial
pressures, predominates in the cerebral circulation but is
not as critical in other tissue beds. Autoregulation and CO2
responsiveness are both blunted in the fetal and immature
brain [107].

**KEY POINTS: REGULATION OF VASCULAR TONE IN SYSTEMIC AND PULMONARY CIRCULATIONS**

- The pulmonary vascular endothelium exerts major
control of vascular tone and resistance, maintaining
low resistance through complex pathways, including
nitric oxide, prostaglandins, and cGMP.
- Systemic vascular tone and resistance are main-
tained in a higher resistance state than the
pulmonary vascular circulation with more
neurohormonal activation that includes the symp-
thoadrenal, renin–angiotensin–aldosterone, and
phospholipase-C systems.
- Pathophysiologic derangements in vascular tone of
pulmonary and systemic circulations have led to
therapeutic approaches such as inhaled nitric oxide
and endothelin receptor antagonists.
Receptor signaling in myocardial dysfunction, CHD, and heart failure

A discussion of receptor signaling and calcium cycling in myocardial dysfunction is useful to serve as the basis for understanding many of the therapies discussed later in this text, and this section will focus on receptor physiology and calcium flux in three settings: acute myocardial dysfunction as seen after cardiac surgery and cardiopulmonary bypass, changes seen as responses to chronic cyanotic heart disease, and those seen with chronic congestive heart failure and cardiomyopathy.

Receptor signaling in acute myocardial dysfunction

Acute myocardial dysfunction, such as that sometimes seen after cardiopulmonary bypass, is often treated with catecholamines. These drugs are sometimes ineffective, especially when used in escalating doses. In children, the number and subtype distribution of ß-adrenergic receptors in atrial tissue are not affected by cardiac surgery with bypass; however, the activation of adenylate cyclase by isoproterenol is significantly reduced after bypass [108]. There is an uncoupling of ß receptors from the Gs–protein–adenylate cyclase complex. Desensitization to moderate or high doses of catecholamines may occur after only a few minutes of administration, because increased cAMP concentrations result in uncoupling from the Gs protein [109].

Only a few minutes of high-dose catecholamine administration may result in inactivation of the phosphorylated adrenergic receptors from sequestration. These receptors can be sequestered by endocytosis, in a process involving a protein called ß-arrestin, which binds to the receptor and a sarcolemmal protein called clathrin (Figure 5.15) [50]. These sequestered receptors may be either recycled back to the cell membrane surface or destroyed by lysosomes [110]. This permanent destruction and degradation of receptors occurs after hours of exposure to catecholamines and is accompanied by decreased mRNA and receptor protein synthesis, resulting in prolonged decrease in adrenergic receptor concentrations, which is reversed by decreasing exogenous catecholamines, but only as fast as new receptors can be synthesized.
Neonatal hearts may exhibit a different response to the acute or prolonged administration of catecholamines. Instead of desensitization, neonatal animal models demonstrate an enhanced β-adrenergic receptor response, accompanied by an increase in adenylate cyclase activity [111]. Desensitization as described occurs later in development. The exact translation of these data to humans is not clear.

Treatment with catecholamines may also increase the concentration of Gᵢ protein subunits, decreasing the sensitivity of the β-adrenergic receptor. This relative decrease in the ratio of Gₛ to Gᵢ protein subunits has been demonstrated in rat and dog models [112,113]. Another possible mechanism of catecholamine-induced desensitization of the neonatal myocyte was demonstrated in a rat model, where prolonged exposure to norepinephrine caused an initial increase in functional L-type Ca²⁺ channels on the sarcolemmal membrane. Continued exposure caused a decrease in L-type Ca²⁺ channel mRNA to 50% of control values [114]. SERCA concentrations are reduced with chronic norepinephrine administration in the dog [115]. Finally, exposing adult or neonatal rat myocytes to high concentrations of catecholamines for 24 hours leads to increased apoptosis of myocardial cells, a genetically programmed energy-dependent mechanism for cell death and removal [116,117]. This effect was mediated through β-adrenergic receptors in the adult model, and α receptors in the neonatal model.

All of these studies provide the theoretical basis for the argument that administration of catecholamines to patients with acute myocardial dysfunction should be limited in dose and duration. Obviously, this is difficult to accomplish in the setting of weaning a hemodynamically unstable patient from cardiopulmonary bypass. Strategies that may limit catecholamine dose include administering low doses of catecholamines together with phosphodiesterase inhibitors, as well as adding corticosteroids, tri-iodothyronine, and vasopressin [118].

**Receptor signaling in CHD**

In the past decade, new information has come to light concerning adrenergic receptor signaling in patients with CHD. A study of 71 infants and children undergoing cardiac surgery used tissue from the right atrial appendage to study β-adrenergic receptor density, distribution of β₁ and β₂ receptor subtypes, and coupling to adenylate cyclase [119]. This study found that patients with severe, or poorly compensated cyanotic (e.g. congestive heart failure) or cyanotic (e.g. severe cyanosis) disease had significantly reduced β-adrenergic receptor densities. Outside of the newborn period, this downregulation was β₁-selective, but
in newborns with critical aortic stenosis or transposition of the great arteries, there was additional significant down-regulation of the β₂ subtype. In tetralogy of Fallot patients, those treated with propranolol had a significant increase in the number and density of β-adrenergic receptors, when compared with untreated patients. Beta-adrenergic receptor downregulation was correlated with increased circulating norepinephrine levels. Finally, in severely affected patients, adenylate cyclase activity was reduced, demonstrating a partial decoupling, as noted earlier. Other studies have determined that symptomatic tetralogy of Fallot patients (i.e., those with cyanotic spells) have a significantly greater number of β-adrenergic receptors in their right ventricular outflow tract muscle, and their adenylate cyclase activity was greater than that in patients without cyanotic spells [120]. Alpha-1-adrenergic receptors are also affected by CHD. A study of atrial tissue excised at surgery in 17 children evaluated α- vs. β-adrenergic receptor stimulation with pharmacologic agents. The α component was responsible for 0–44% of the inotropic response, and β stimulation for 56–100% of the response, with the degree of right ventricular hypertrophy and pressure load correlating with the amount of a stimulation found [121].

**Receptor signaling in congestive heart failure and cardiomyopathy**

Like adults with heart failure, children with congestive heart failure due to chronic left-to-right shunting and volume overload of the heart have elevated levels of circulating norepinephrine. This leads to a downregulation in β-adrenergic receptor density [122]. The degree of elevation of pulmonary artery pressure and amount of left-to-right shunting correlates with the plasma catecholamine levels and is inversely correlated with β-adrenergic receptor density. All of these abnormalities return to normal levels after corrective surgery. The degree of receptor downregulation in congestive heart failure is correlated with postoperative morbidity in infants and children. Children with an intensive care unit stay of greater than 7 days or those who died during the early postoperative period (nine of 26) had significantly less β₁ and β₂ mRNA gene expression than those who had better outcomes [123]. In addition, the children receiving propranolol for treatment of their congestive heart failure had higher β-adrenergic receptor mRNA levels and tended to have improved outcomes. Finally, children with dilated cardiomyopathy also have a reduced response to catecholamines, with one study showing no significant increase in ejection fraction during dobutamine stress test, with infusion of dobutamine at 5 and then 10 μg/kg/min [124]. Generally, studies in excised right atrial tissue in infants and children with CHD or cardiomyopathy demonstrate decreased density of β₁ and β₂ receptors, and decreased downstream adenylate cyclase function, with larger decreases associated with worse ventricular function [125].

This has been a brief discussion of receptor signaling in pediatric heart disease. This emerging field has many implications for treatment strategies, and the reader is referred to excellent reviews for more detail information on this subject [126].

**KEY POINTS: RECEPTOR SIGNALING IN MYOCARDIAL DYSFUNCTION, CHD, AND HEART FAILURE**

- High catecholamine doses in acute myocardial dysfunction can desensitize the myocardium though uncoupling of G-protein adenylate cyclase complex, and sequestration of β-adrenergic receptors.
- Significant cyanotic or acyanotic CHD with heart failure can result in down-regulation of β-adrenergic receptors in neonatal or infant myocardium.
- Longstanding decreased ventricular function are often associated with decreased density of β-adrenergic receptors and decreased adenylate cyclase function.

**Myocardial preconditioning**

Myocardial preconditioning refers to the finding that repeated, brief exposures of the myocardium to ischemia, volatile anesthetics, or other stresses induces a protective effect to a later (i.e. 12–24 hours), more prolonged, ischemic insult, resulting in decreased myocardial infarction size and improved myocardial function after the insult [127]. Chronic cyanosis also induces a similar protective effect in the myocardium, although the effect size is smaller and more long-lasting (i.e., beyond 24 hours). Another mechanism is remote ischemic preconditioning (RIPC), in which ischemia is produced in a tissue bed remote to the myocardium, for example skeletal muscle of the arm or leg by repeated inflation of a blood pressure cuff which is thought to liberate as yet uncharacterized neurohumoral or hormonal substances that can protect the myocardium (Figure 5.16) [128]. The mechanisms of myocardial preconditioning are complex, but are thought to involve release of various neurohumoral agents and peptides such as adenosine, bradykinin, and nitric oxide via a cGMP-dependent mechanism, which then triggers a series of signal transduction events within the cardiomyocyte that confer a “memory” effect that protects the myocardium from future ischemic insults. The signal transduction effects include PKC, tyrosine kinases, mitogen-activated protein kinases, glycogen synthase kinase 3β, and other enzymes [129]. This series of events allows activation of mitochondrial and sarcoplasmic reticulum K<sub>ATP</sub> channels, which leads to the preconditioning by elusive mechanisms. One recently discovered candidate for this end effector is the mitochondrial permeability transition pore (MPTP) [129]. This is a non-specific channel that
spans both mitochondrial membranes, and when opened for a prolonged period results in a dissipation of mitochondrial electrical potential, inhibition of ATP synthesis, and ultimately mitochondrial swelling, rupture, failure of cellular energy metabolism, and cell death. Agents and stimuli that confer myocardial preconditioning have been found to keep the MPTP closed, thus possibly elucidating further the subcellular mechanisms involved.

Several recent pediatric cardiac surgery studies have been published elucidating the potential effects of myocardial preconditioning, which could have the beneficial effect of ameliorating the myocardial stunning effect seen in operations on infants with long aortic cross-clamp times [130]. In a study of 90 infants randomized to sevoflurane, propofol, or midazolam anesthesia for maintenance, plus a sufentanil infusion for analgesia, patients receiving sevoflurane had a very strong trend toward lower troponin T concentrations in the first 24 hours after surgery, potentially signifying less myocardial injury due to the pre-bypass exposure to sevoflurane [131]. Remote ischemic preconditioning produced by inflating a blood pressure cuff on a lower extremity to produce a 5-minute period of limb ischemia, for four cycles before cardiopulmonary bypass, was studied in 37 children undergoing cardiac surgery. Patients who underwent RIPC had lower peak troponin I levels (17 vs. 22 μg/L, P = 0.04), and lower inotrope score in the RIPC group at both 3 and 6 hours post-bypass [132]. This interesting phenomenon of RIPC may work via modulation of the inflammatory response through some as yet unknown humoral mechanism. Some recent small controlled trials of RIPC in children measured inflammatory and myocardial injury markers such as tumor necrosis factor-alpha and interleukins (ILs). Several of these studies demonstrated decreases in creatine kinase, inflammatory mediators IL-8 and -10, heat shock protein, and cardiac enzymes creatine kinase and troponin I with RIPC. However, none of these studies demonstrated a clinical difference in ventilation time, intensive care unit stay, end-organ dysfunction, or death [133–136]. Thus it would appear that despite the initial enthusiasm for this relatively simple clinical intervention, the studies to date demonstrate no clinical benefit. The exact mechanisms of RIPC are still not completely elucidated, and the small muscle mass of infants and children compared with adults, the different clinical approaches to anesthetic agent and corticosteroid use, and the small numbers of patients studied to date may prevent conclusive data. More study is required before RIPC could be recommended for clinical use, if ever.

**KEY POINTS: MYOCARDIAL PRECONDITIONING**

- Myocardial preconditioning is a complex phenomenon by which repeated brief exposure of the myocardium to ischemia or other stresses induces a protective effect to later ischemic insults.
- The mitochondrial permeability transition pore is a common pathway for the various forms of ischemic

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Figure 5.16 Biological effects of remote ischemic preconditioning. Transient ischemia of the arm liberates a circulating effector that induces remote cellular adaptation to a subsequent, extended, and potentially lethal period of ischemia in remote tissues. (Source: Kharbanda et al. [128]. Reproduced with permission of Elsevier.)
preconditioning, staying closed and preventing mitochondrial failure.

- Remote ischemic preconditioning produced by inflation of a blood pressure cuff on a limb before CPB will reduce some inflammatory and ischemic cell death markers, but as yet has not improved clinical outcomes.

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http://www.wiley.com/go/andropoulos/congenitalheart


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The pharmacologic approaches are reviewed in the latter half of the paper.

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CHAPTER 6
Anesthetic Agents and Their Cardiovascular Effects

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Introduction

A wide variety of anesthetic regimens are used for patients with congenital heart disease (CHD) undergoing cardiac or non-cardiac surgery, procedures in the cardiac catheterization laboratory, or other diagnostic or therapeutic procedures such as magnetic resonance imaging (MRI). The goal of all of these regimens is to produce general anesthesia or adequate sedation, while preserving systemic cardiac output (CO) and oxygen delivery. Many of these patients have limited cardiac reserve, and if a cardiac arrest or other adverse cardiac event occurs, successful resuscitation is less frequent than in patients with normal hearts [1]. Thus, intelligent selection of regimen and dosage, with the patient’s unique pathophysiology in mind, along with anesthetic requirements for the particular procedure they are undergoing, is essential. This chapter reviews the effects on hemodynamics and myocardial contractility of anesthetic agents and muscle relaxants commonly used for patients with CHD.

Volatile agents

Although halothane has not generally been available in the US for the past decade, it is still used in some parts of the world, and it serves as the basis for comparison with newer agents because of the number of studies of its hemodynamic effects in children with and without heart disease. Therefore data concerning halothane will be presented in this section. In vitro studies of effects on contractility in isolated adult human atrial fibers indicate that direct myocardial contractility depression is at its greatest with halothane and that sevoflurane is equal to isoflurane and desflurane [2] (Figure 6.1). These studies of myocardium reveal that differences among these agents occur primarily from differing effects on calcium flux through L-type Ca^{2+} channels, both transarcolemmal and in the sarcoplasmic reticulum (SR). Halothane reduces Ca^{2+} flux through the sarcolemma more than isoflurane, with the net result that there is less intracellular Ca^{2+} available to bind to the troponin–actin–myosin complex which produces myocyte contraction. Another mechanism of myocardial depression is that halothane, but not isoflurane, directly activates ryanodine-sensitive SR Ca^{2+} channels, thereby reducing Ca^{2+} storage in the SR and making it less available for release during contraction. The effects of sevoflurane and desflurane on Ca^{2+} flux are similar to those of isoflurane [2].

It is important to note that infants from the newborn period up to an age of approximately 6 months exhibit an exaggerated degree of depression of myocardial

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contractility and blood pressure in response to all volatile agents, but especially halothane [3,4] (Figure 6.2). This is probably due to the immaturity of the Ca\(^{2+}\) release and reuptake system, necessitating higher levels of free cytosolic Ca\(^{2+}\) to be available to bind to the troponin–actin–myosin complex to produce myocyte contraction [5]. Recent evidence supports this theory. Sevoflurane, and to a greater extent halothane, interferes with both L-type Ca\(^{2+}\) channel and Na\(^+\)/Ca\(^{2+}\) exchanger Ca\(^{2+}\) flux at the plasmalemmal membrane more in neonatal than in adult rat myocytes [6]. The volatile anesthetics interfered with Ca\(^{2+}\) release from the SR more in adult rat myocytes. This information provides a mechanism for what is commonly observed clinically.

The effects of volatile agents on systemic vascular resistance (SVR), as measured by arterial blood pressure, differ between agents. Ca\(^{2+}\) flux in the smooth muscles of arterioles is reduced by all of these agents, resulting in less resting tone and thus lower blood pressure and vascular resistance. Halothane exhibits the most pronounced reduction of blood pressure, due to the combination of reduction in arterial tone, as well as the more pronounced depression of myocardial contractility. Isoflurane and sevoflurane lower blood pressure primarily through reduction in SVR [7].

Sevoflurane has largely replaced halothane throughout most of the world for induction and maintenance of anesthesia. The Pediatric Perioperative Cardiac Arrest Registry data demonstrated a decrease in anesthetic medication-related cardiac arrests, from 37% of the total in 1994–97 to 18% in 1998–2004; the authors primarily attributed this decrease to the less frequent use of halothane, leading to fewer arrests, particularly in young infants [8].

In patients with CHD, several studies have been performed comparing new agents with halothane. A study using transthoracic echocardiography comparing halothane, isoflurane, and sevoflurane [7] in 54 children with two-ventricle CHD (Table 6.1, Figure 6.3) reported that 1 and 1.5 MAC (minimum alveolar concentration) halothane caused significant myocardial depression, resulting in a decrease in mean arterial pressure (MAP, decline of 22% and 35%, respectively), ejection fraction (EF, decrease of 15% and 20%, respectively) and CO, decrease of 17% and 21%, respectively) in patients aged 1 month–13 years undergoing cardiac surgery. Sevoflurane maintained both CO and heart rate (HR), and had less profound hypotensive (MAP decrease 13% and 20% at 1 and 1.5 MAC, respectively) and negative inotropic (EF preserved at 1 MAC, 11% decrease at 1.5 MAC) effects than halothane. Isoflurane, in concentrations as high as 1.5 MAC, preserved CO and EF, caused less suppression of MAP (22% and 25%) than halothane, increased HR (17% and 20%) and decreased SVR (20% and 22%).

The effects of these agents on pulmonary (Qp) and systemic blood flow (Qs) in 30 biventricular patients and left-to-right shunts have also been assessed. Halothane, isoflurane, and sevoflurane did not change Qp:Qs as measured by echocardiography [9]. Russell et al. [10] compared halothane with sevoflurane in the pre-bypass period in 180 children with a variety of cardiac diagnoses, including 14 with single-ventricle physiology and 40 with tetralogy of Fallot (TOF). The incidence of significant hypotension, bradycardia, and arrhythmia requiring drug treatment with atropine, phenylephrine, epinephrine, or ephedrine was higher with halothane (two events per patient vs. one with sevoflurane). Serum lactate also increased slightly with halothane.

In a randomized crossover comparison study of 1 MAC isoflurane vs. sevoflurane, Dalal et al studied 10 children with a variety of CHD, with both single- and two-ventricle diseases [11]. Stroke volume, EF, and cardiac index were determined for the systemic ventricle using cardiac MRI techniques. There were no differences between agents for these parameters, or differences in MAP or HR in this small study. Wang et al. assessed differences in HR, cardiac rhythm, and blood pressure in 55 infants aged 2–12 months during 8% sevoflurane induction [12]. Twenty-nine had increased pulmonary blood flow (PBF) (atrial septal defect [ASD], ventricular septal defect [VSD], patent ductus arteriosus [PDA]), and 26 decreased PBF (TOF, pulmonic stenosis). The first 10 minutes of the anesthetic were assessed, and differences between groups compared. HR decreased from baseline in both groups, with a greater decrease in patients with decreased PBF. Blood pressure decreased significantly in the increased PBF group, but was unchanged in the patients with
Figure 6.2 Force of contraction (N/cm²) in neonatal vs. adult rat ventricular trabecular muscle. Baseline force of contraction is greater in adult tissue, and both halothane and sevoflurane depress contractility more in the neonatal than in adult ventricular muscle. Halothane depresses contractility to a greater extent in both age groups. Panels A and B report raw data, while panels C and D express results as a percentage of baseline contractility. *Indicates a significant difference between ages (P < 0.05; n = 12 for controls, and n = 6 for all other groups). † Indicates a significant difference between control and halothane groups. ‡ Indicates a significant difference between 1 and 2 minimum alveolar concentration (MAC) anesthetic.

(Source: Prakash et al. [4]. Reproduced with permission of Lippincott Williams & Wilkins.)

Table 6.1 Hemodynamic changes in response to four anesthetic regimens in 54 children with congenital heart disease with two ventricles

<table>
<thead>
<tr>
<th>Agent</th>
<th>MAC (beats/min)</th>
<th>MAP (mmHg)</th>
<th>EF (%)</th>
<th>SF (%)</th>
<th>SVI (ml/m²)</th>
<th>LVEDVI (ml/m²)</th>
<th>CI (L/min/m²)</th>
<th>SVRI (dyn s/cm⁵/m²)</th>
</tr>
</thead>
<tbody>
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<tr>
<td>0</td>
<td>129 ± 22</td>
<td>77 ± 15</td>
<td>63 ± 9</td>
<td>40 ± 5</td>
<td>36 ± 16</td>
<td>44 ± 19</td>
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<tr>
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<td>130 ± 19</td>
<td>60 ± 11*</td>
<td>54 ± 12*</td>
<td>32 ± 7*</td>
<td>28 ± 11*</td>
<td>38 ± 14</td>
<td>3.47 ± 1.17</td>
<td>1331 ± 529</td>
</tr>
<tr>
<td>1.5</td>
<td>129 ± 17</td>
<td>49 ± 12*</td>
<td>50 ± 13*</td>
<td>30 ± 8*</td>
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<td>3.34 ± 1.36*</td>
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<td>68 ± 11</td>
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<td>62 ± 9</td>
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<td>36 ± 18</td>
<td>6.59 ± 4.04</td>
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<td>43 ± 30</td>
<td>52 ± 24</td>
<td>3.67 ± 2.99*</td>
<td>1559 ± 875</td>
</tr>
</tbody>
</table>

All values are means ± SD.

*P < 0.05, one-way analysis of variance (ANOVA), different from 0 minimum alveolar concentration (MAC) within the same anesthetic group.

†P < 0.05, two-way ANOVA, halothane vs. sevoflurane and fentanyl–midazolam at 1 and 1.5 MAC.

‡P < 0.05, two-way ANOVA, fentanyl–midazolam vs. halothane at 0 MAC.

§P < 0.05, two-way ANOVA, fentanyl–midazolam vs. halothane, sevoflurane, and isoflurane at 1.0 and 1.5 MAC. CI, systemic cardiac index; EF, ejection fraction; HR, heart rate; LVEDVI, left ventricular end-diastolic volume index; MAP, mean arterial pressure; SF, shortening fraction; SVI, stroke volume index; SVRI, systemic vascular resistance index.

Source: Rivenes et al. [7]. Reproduced with permission of Lippincott Williams & Wilkins.
decreased PBF. Junctional rhythm was observed in one patient in the increased PBF group.

Patients with a single functional ventricle comprise an increasing proportion of patients undergoing anesthetics for both cardiac and non-cardiac surgery, and studies of the hemodynamic effects of anesthetic agents are limited. Ikemba et al. [13] studied 30 infants with a single functional ventricle immediately before their bidirectional cavopulmonary connection, randomized to receive sevoflurane at 1 and 1.5 MAC, or fentanyl/midazolam at equivalent doses. Myocardial performance index (MPI), a transthoracic echocardiographic measurement of ventricular function that can be applied to single-ventricle patients, was not changed with any of these regimens when compared with baseline, indicating that either sevoflurane or fentanyl/midazolam can be used in this population to maintain hemodynamic stability.

In normal children, desflurane commonly produces tachycardia and hypertension during the induction phase, followed by a slight reduction in HR and systolic blood pressure during steady state at 1 MAC anesthetic level [14,15]. There are no reports of its hemodynamic profile in patients with CHD. In a study of 47 children (mean age 12.8 years) undergoing electrophysiological study for supraventricular tachycardia (SVT), desflurane allowed induction of the SVT in all patients, and demonstrated no clinically important differences in any electrophysiological measurement, as compared with a fentanyl-based anesthetic [16]. The very low arrhythmogenic potential of desflurane has been demonstrated to be similar to that of isoflurane [17].

Some patients (6–12%) exposed to sevoflurane develop arrhythmias, mostly atrial or junctional [18,19]. A study performed in infants (mean age 7.5 months) found that sevoflurane induction caused a 20% incidence of junctional bradycardia (less than 80 beats/min). Isoflurane, when utilized in children for electrophysiologic studies and radiofrequency ablation for SVT, does not affect sinoatrial or atrioventricular (AV) node conduction, and all arrhythmias were easily induced [20]. There are case reports of sevoflurane causing torsade de pointes in children with congenital long QT syndrome; this effect may be due to the increased HR often seen with induction of anesthesia with this agent [21]. In a study of sevoflurane inhalation induction using electronic anesthesia data, Kraemer et al. compared 209 children with Down syndrome with or without CHD with 268 healthy controls without Down syndrome or CHD. Fifty-seven percent of the Down syndrome patients experienced age-defined hypotension and bradycardia during the first 6 minutes of anesthesia, as compared with 12% of patients without Down syndrome or CHD (odds ratio, 9.56; 95% confidence interval 6.06–15.09) [21]. Bradycardia was not further characterized, i.e. sinus vs. junctional.

Few studies to date have addressed the effects of the different anesthetics on an important group of pediatric patients with heart disease: patients with cardiomyopathy or significantly decreased systolic ventricular function. Volatile agents were commonly employed in two retrospective series of anesthesia in children with cardiomyopathy. Lynch et al. administered volatile agents in 26% of 236 inductions, and only four patients (1.7%) had cardiac arrest on induction; none of the four received volatile agents [22]. Kipps et al. reported a series of 33 children; 12% received volatile agents for induction and 64% received them for maintenance [23]. Although there were 15 patients with severe complications, defined as significant hypotension, arrhythmia, cardiac arrest, extracorporeal membrane oxygenation cannulation, or death,
no conclusions could be drawn about any association with use of volatile agents. Rather, severe ventricular dysfunction (shortening fraction <16%) was the most important predictor of complications. Diastolic function with halothane and isoflurane has been studied in animal models of cardiomyopathy [24,25]. The two agents differ, with halothane producing negative lusitropic effects, while isoflurane conserves or may even improve diastolic function. There are no reports measuring diastolic function in response to anesthetic agents in patients with CHD.

KEY POINTS: VOLATILE AGENTS

- Depression of myocardial contractility and CO is greatest with halothane, minimal with sevoflurane, and least with isoflurane and desflurane at end-tidal concentrations up to 1.5 MAC.
- All volatile agents may depress myocardial contractility and CO at high doses; infants less than 6 months of age are at greatest risk.
- Patients with significantly decreased ventricular systolic function are presumed to be at greatest risk for further myocardial depression from any volatile agent.

Nitrous oxide ($N_2O$)

Despite its ubiquitous use as an adjunct to anesthetic induction and maintenance in patients with CHD, information regarding the effect of $N_2O$ on hemodynamics in patients with CHD is very limited. Its use may be relatively contraindicated where increased $FiO_2$ is employed, or where enlargement of enclosed air collections is possible, such as in any intracardiac or intrathoracic surgery. Reports of increased pulmonary vascular resistance (PVR), sympathetic stimulation, or significantly decreased CO in response to $N_2O$ in adult patients have not been substantiated in children with or without cardiac disease [26,27].

In infants and small children with normal hearts, Murray et al. found that addition of 30% and 60% $N_2O$ to 1 MAC halothane or isoflurane resulted in a decreased HR and cardiac index, without changing EF and stroke volume measured echocardiographically [28]. These authors also demonstrated that when 0.6 MAC halothane or isoflurane was substituted for 60% $N_2O$ during 0.9 MAC isoflurane or halothane anesthesia, HR, MAP, and cardiac index were unchanged [29].

In 14 patients with CHD recovering from surgery, Hickey et al. [30] administered 50% $N_2O$ and observed a decrease of 9% in HR 12% in MAP and 13% in systemic cardiac index. However, mean pulmonary artery pressure and PVR were not significantly changed in these well-ventilated patients with a $PaCO_2$ of 34–35, and pH of 7.47–7.49, even in patients with elevated PVR at baseline. This single report represents the total number of patients with CHD in which $N_2O$ administration has been carefully studied. Despite this paucity of information, extensive clinical experience has demonstrated $N_2O$ to be safe and effective, particularly as an adjunct to inhaled induction of anesthesia for congenital heart surgery.

Opioids and benzodiazepines

Fentanyl and sufentanil have been studied as a sole anesthetic in patients with CHD. Hickey, Hansen and colleagues [31–34] provided the basis for this technique with a series of studies in neonates and infants less than 1 year of age undergoing complex repairs, ranging from the Norwood operation to complete repair of biventricular lesions. Fentanyl doses of 50–75 $\mu$g/kg, and sufentanil doses of 5–40 $\mu$g/kg, administered with pancuronium 0.1–0.15 mg/kg, provided excellent hemodynamic stability with minimal changes in HR and blood pressure throughout the surgery. The increase in pulmonary artery pressure and resistance in response to suctioning in infants recovering from cardiac surgery was eliminated with 25 $\mu$g/kg fentanyl. Moore et al. [35] demonstrated that 5, 10, or 20 $\mu$g/kg sufentanil in children aged 4–12 years had no effect on EF as measured by echocardiography, in patients undergoing repair of biventricular lesions. Increases in HR, blood pressure, and stress hormones were more effectively blunted by the higher doses. Glenski et al. [36] reported M-mode echocardiographic measures of contractility, blood pressure, and HR response using fentanyl (at 100 $\mu$g/kg) or sufentanil (at 20 $\mu$g/kg) in children aged 6 months–9 years. Measurements were made at three different times: after a premedication with morphine and scopolamine, after induction, and after tracheal intubation. These opioids decreased both EF and shortening fraction after induction, but they returned to or above baseline after intubation.

Midazolam is often added to fentanyl anesthesia to provide sedation and amnesia, as a substitute for low-dose volatile anesthetic agent, particularly in hemodynamically unstable patients and young infants, where the myocardial depressant effects of volatile agents are more pronounced. Fentanyl and midazolam combinations have been studied in two different clinically utilized dose regimens to simulate 1 and 1.5 MAC of volatile agents (fentanyl 8–18 $\mu$g bolus followed by 1.7–4.3 $\mu$g/kg/hour infusion, then repeat bolus at 50% of the original doses followed by increase of infusion by 50%, depending on age; midazolam 0.29 mg/kg bolus followed by 139 $\mu$g/kg/hour infusion, then repeat bolus 50% of the original dose, followed by increase in infusion of 50% for all ages) for induction and the pre-bypass period in congenital heart surgery in biventricular patients [7] (Figure 6.3). Vecuronium was used for muscle relaxation in order to isolate the effects of
Chapter 6 Anesthetic Agents and Their Cardiovascular Effects

the other two agents on hemodynamics. Measurements of CO and contractility were made by echocardiography. Fentanyl/midazolam caused a significant decrease (22%) in CO despite preservation of contractility. This was predominantly due to a decrease in HR. Co-administration of a vagolytic agent such as atropine [37] or pancuronium would probably preserve CO. The added effect of midazolam on echocardiographic indices of contractility has not been previously reported; however, increased inotropic support requirements have been documented in infants undergoing cardiac surgery with the addition of midazolam bolus totaling 0.3 mg/kg, and infusion of 0.1 mg/kg/hour intraoperatively [38].

The stress response to major cardiac surgery in infants and children has been the subject of considerable interest. Anand and Hickey reported the use of high-dose sufentanil at a total mean dose of 37 μg/kg as a sole anesthetic for complex neonatal surgery [39]. The sufentanil was continued by infusion for 24 hours postoperatively. This regimen was compared with halothane plus morphine (mean dose of 0.35 mg/kg) intraoperatively, followed by intermittent morphine and diazepam postoperatively. Stress response, as measured by changes in adrenal hormones: cortisol, glucose, and lactate, was significantly reduced in the sufentanil group, and mortality and major complications such as sepsis and necrotizing enterocolitis were also significantly reduced. A more recent study from the same institution of 45 infants averaging 3 months of age undergoing biventricular repair has been reported [38]. A fentanyl total dose of 100 μg/kg was administered, given either as intermittent boluses of 25 μg/kg or as boluses plus infusion, with or without midazolam, and all regimens resulted in a significant endocrine stress response to cardiac surgery. Despite this, the outcome was excellent in all groups, with no adverse outcomes related to the anesthetic technique or to stress response. The sole hemodynamic difference between the regimens was a lower MAP during cooling on bypass in the group who received midazolam. Finally, Duncan et al. [40] reported a dose–response study of 2, 25, 50, 100, and 150 μg/kg fentanyl before bypass in 40 children averaging 13 months and 8.5 kg. The 2 μg/kg group had significant increases in pre-bypass norepinephrine, glucose, and cortisol, and significantly higher HR and blood pressure than all other groups. A dose of 25 μg/kg or higher eliminated changes in these parameters for the duration of the surgery. It is difficult to interpret the significance of these stress response studies because they were evaluated by different age groups and lesions. Also there was more than one decade between reports, during which time there were significant improvements in surgical, bypass, and postoperative management. If any group of patients had benefited from attenuation of the stress response, it would appear to be neonatal patients undergoing complex surgery. Current approaches to early extubation favor lower intraoperative opioid doses, e.g. 10–20 μg/kg fentanyl, and use of adjuvants such as dexmedetomidine or regional anesthesia, rather than completely ablating the stress response [41]. Chapter 20 presents an extensive discussion of early extubation approaches for congenital cardiac surgery.

Remifentanil is a synthetic ultra-short-acting narcotic agent metabolized by plasma esterases with a half-life of 3–5 minutes that is independent of the duration of infusion [42]. It is particularly useful for short non-cardiac procedures with intense stimulation where opioid-based anesthesia and its hemodynamic stability would be desirable, yet where rapid emergence is also important. Donmez et al. [43,44] reported a series of 55 children undergoing cardiac catheterization with a remifentanil infusion of 0.1 μg/kg/min. This regimen maintained excellent cardiovascular stability, with minimal changes in HR, blood pressure, or oxygen saturation. Fifty-eight percent of patients required additional sedation with midazolam or ketamine. Apnea was infrequent, and a time to recovery score of 5 (10-point scale) was only 2–4 minutes. Patients undergoing long cardiac catheterization procedures could potentially benefit from this agent.

Remifentanil infusion at 0.3 μg/kg/min increased sinus cycle and Wenckebach cycle length from baseline, but did not affect atrial-His or His-ventricular interval, or AV node, atrial, ventricular, or accessory pathway effective refractory period in 14 patients undergoing electrophysiology study and ablation for SVT [45]. In a similar study of 29 patients receiving 0.2 or 0.4 μg/kg/min remifentanil, the larger dose prolonged sinoatrial conduction time and sinus node recovery time, but not atrial-His interval [46]. These electrophysiological effects should be taken into account if the drug is used for electrophysiological studies.

Remifentanil administration has been reported for ASD repair, where patients are extubated in the operating room (OR) [47]. It apparently does not bind to the cardiopulmonary bypass (CPB) circuit [48] and its clearance in children before and after CPB appears to be predictable within a narrow range, making it a potentially useful agent for "fast-track" anesthesia and early extubation for simple surgical procedures. Freisen et al. compared remifentanil 0.3–0.7 μg/kg/min with fentanyl 15 μg/kg, both with isoflurane and pancuronium, in fast-track pediatric cardiac operations (ASD and VSD repairs), and found that HR was significantly slower in the OR in the remifentanil group, but there was no difference in time to extubation, analgesic requirements in ICU, nausea/vomiting or hypertension in ICU, or in ICU length of stay [49]. Akpek et al. compared higher-dose remifentanil (2 μg/kg load and 2 μg/kg/min maintenance infusion) with fentanyl (20 μg/kg load and 20 μg/kg/hour infusion) in 33 infants with pulmonary hypertension undergoing surgery for repair of left-to-right shunting defects. Both groups had a midazolam infusion. There were no clinically important differences in hemodynamic, respiratory, or oxygen saturation parameters between groups, and no difference in clinical outcomes [50]. Thus, despite some theoretical advantages due to its pharmacokinetic profile, there are few clinically significant differences between remifentanil and fentanyl.
KEY POINTS: OPIOIDS AND BENZODIAZEPINES

- Fentanyl, sufentanil, and remifentanil have minimal effect on myocardial function, even at large doses.
- Synthetic opioids decrease catecholamine release and other measures of stress response, including pulmonary hypertension, at moderate and large doses.
- Complete ablation of the stress response with large opioid doses is employed less often in recent years without decrement in outcomes.
- Midazolam (and other benzodiazepines) in large doses may increase inotropic support needs in infants.

Propofol

Propofol has become a popular agent for sedation for cardiac catheterization procedures and induction of general anesthesia for cardiac surgery. In plasma concentrations found in routine clinical use, propofol has minimal negative inotropic effects in isolated animal cardiac preparations [51] or in human adult atrial muscle strips [52].

In children with normal hearts, propofol at induction doses consistently decreases systolic and mean arterial pressure by 5–25% without changing HR [53]. In a case series of 13 preterm neonates of 29–32 weeks gestational age, a propofol bolus of 1 mg/kg decreased MAP from 38 to 24 mmHg, and five of 13 patients had a severe decrease to <25 mmHg [54]. There has been one published study using echocardiography to assess myocardial contractility and CO in infants with normal hearts induced with propofol [53]. The shortening fraction or cardiac index was not changed, and SVR decreased by 14% and 27% at 1 and 5 minutes after induction, respectively. Load independent measures of contractility (stress velocity index and stress shortening index) decreased significantly from baseline at 5 minutes after induction with propofol.

Williams et al. [55] measured the hemodynamic effects of propofol in 31 patients aged 3 months–12 years at a dose of 50–200 μg/kg/min undergoing cardiac catheterization. (Figure 6.4). They found that propofol significantly decreased MAP and SVR; however, there was no change in systemic CO, HR, and mean pulmonary artery pressure, as well as PVR. In patients with cardiac shunts, the net result was a significant increase in the right-to-left shunt, a decrease in the left-to-right shunt, and decreased Qp:Qs, resulting in a statistically significant decrease in PaO₂ and SaO₂, as well as reversal of the shunt from left-to-right to right-to-left in two patients. In another study of patients undergoing cardiac catheterization, Lebovic et al. [56] demonstrated that patients could experience a 20% decrease in HR or MAP. Recently, combining propofol infusion with ketamine infusion for cardiac catheterization procedures demonstrated less change in MAP, preservation of baseline HR, and little effect on recovery time [57].

Propofol has no significant effect on sinoatrial or AV node conduction, or on the ability to induce SVT, and therefore is desirable as a primary agent during electrophysiologic studies and radiofrequency ablation [20,58]. However, ectopic atrial tachycardia may be suppressed by propofol [59].

Although propofol is very useful for cardiac catheterization, short, stimulating procedures, and possibly for short-term sedation after cardiac surgery, its use long term as an ICU sedative is contraindicated, with several reports of otherwise unexplained metabolic acidosis and myocardial failure after long-term (>48 hours), high-dose use in pediatric patients [60,61]. The mechanism of this cardiovascular collapse is postulated to be due to disruption of fatty acid oxidation caused by impaired entry of long-chain acylcarnitine esters into the mitochondria and failure of the mitochondrial respiratory chain [62]. Although a recent case series of short-term, low- to medium-dose post-anesthetic propofol infusion (median about 6–7 hours) has been described without complication in 12 high-risk patients with pulmonary hypertension, this practice should be limited to those centers with substantial expertise and experience with this technique [63]. Propofol infusions greater than 6 hours’ duration, as might be

![Figure 6.4](image-url) Changes in intracardiac shunting in response to propofol induction and infusion in children undergoing cardiac catheterization. Group 2, patients with net left-to-right cardiac shunting; group 3, patients with net right-to-left cardiac shunting. Qp:Qs decreased significantly in both groups. (Source: Williams et al. [55]. Reproduced with permission of Lippincott Williams & Wilkins.)
observed for long cardiac catheterization procedures, are not recommended because of the potential for the propofol infusion syndrome.

In summary, propofol can be utilized in patients with adequate cardiovascular reserve who can tolerate a mild decrease in contractility and HR, and a decrease in SVR. Propofol may cause an increased intracardiac right-to-left shunt, and reversal of shunt in some patients, (i.e., acyanotic TOF), and thus hemodynamic data obtained in the cardiac catheterization laboratory should be interpreted accordingly. Although propofol use for induction of anesthesia has been described for patients with cardiomyopathies in several case series [22,23], many authorities recommend against its use, particularly in hypertrophic or dilated cardiomyopathy, where even a small reduction in afterload and preload from propofol’s venodilatory properties can result in cardiovascular collapse [64].

**KEY POINTS: PROPOFOL**

- Propofol in induction doses causes a mild decrease in myocardial contractility, but a significant decrease in MAP and HR, as well as some preload reduction from venodilation.
- Propofol infusion has little effect on pulmonary vascular pressure and resistance, but decreases SVR, resulting in an increase in right-to-left shunting.
- Because of its effects to decrease preload, afterload, and myocardial contractility, propofol should be used with great caution if at all in patients with significantly decreased ventricular function, and those with left ventricular outflow obstruction.

**Ketamine**

The general anesthetic and analgesic effects of ketamine are mediated by its interaction with N-methyl D-aspartate receptors in the brain [65]. It increases HR, blood pressure, and CO through central nervous system-mediated sympathomimetic stimulation and inhibition of the reuptake of catecholamines. Ketamine is a direct myocardial depressant when studied in isolated myocyte preparations [66] and in adult human failing atrial and ventricular muscle trabeculae [67] (Figure 6.5). The direct myocardial depression caused by ketamine may be unmasked when administered to patients whose sympathomimetic responses are already maximally stimulated from cardiomyopathy, or another condition leading to poor myocardial reserve, because a further increase in catecholamine release is limited. Similarly, if the patient is chronically receiving β-adrenergic agonists, catecholamine receptors may be downregulated, resulting in a diminished response to endogenously generated catecholamines, allowing the myocardial depressant effects of ketamine to predominate.

The mechanism of myocardial depression is by inhibition of L-type voltage-dependent Ca$^{2+}$ channels in the sarcolemmal membrane. An increased extracellular Ca$^{2+}$ concentration may enhance this effect [68]. This direct myocardial depression effect is greater than that produced by etomidate [52]. In a patient with end-stage cardiomyopathy awaiting heart transplant, hemodynamic collapse occurred after the induction of anesthesia with ketamine [59]. In a study of ketamine vs. sufentanil for induction of anesthesia in patients undergoing cardiac transplant whose average EF was 14%, and who were all receiving inotropes and vasodilators preoperatively, it was found that ketamine increased MAP, central venous pressure, and pulmonary artery pressure significantly, and decreased stroke volume index and left ventricular stroke work index [69]. Cardiac index decreased slightly but not to a statistically significant degree. SVR and HR were higher. The sum total of the hemodynamic effects of ketamine induction in these patients was less myocardial work at the expense of a higher myocardial wall tension. Sufentanil induction did not change any of these parameters from baseline.

Other well-recognized untoward effects associated with ketamine use do not differ among patients with CHD. These include emergence reactions, excessive salivation, and an increase in cerebral metabolism, intracranial pressure, cerebral blood flow and cerebral oxygen consumption [65].

Despite the adverse effects of ketamine, this drug has been a mainstay of induction of general anesthesia...
in patients with CHD [70,71]. Administration can be intravenous (IV) or intramuscular (IM), and it will reliably maintain HR, blood pressure, and systemic CO at an induction dose of 1–2 mg/kg IV or 5–10 mg/kg IM, and a maintenance dose of 1–5 mg/kg/hour in patients with a variety of CHDs, including TOF [72,73] (Figure 6.6). The question about exacerbation of pulmonary hypertension has been addressed in two important studies. Morray et al. [74] demonstrated that in cardiac catheterization patients, 2 mg/kg ketamine caused a minimal (<10%) increase in mean pulmonary artery pressure and in the ratio of PVR to SVR (Rp:Rs), with no change in direction of shunting or Qp:Qs. Hickey et al. [32] studied postoperative cardiac surgery patients with normal PaCO₂ and demonstrated that ketamine 2 mg/kg had no effect on pulmonary artery pressure or calculated PVR, in patients with either normal or elevated baseline PVR. Williams et al. reported that ketamine (2mg/kg load followed by an infusion of 10 µg/kg/min) did not change PVR at all in 15 children with severe pulmonary hypertension, when breathing spontaneously with a baseline of 0.5 MAC sevoflurane [75] (Figure 6.7). Williams et al. also performed a retrospective review of anesthetic technique and outcomes of 92 patients with pulmonary hypertension undergoing 192 anesthetics for non-cardiac surgery, catheterization, and other diagnostic procedures, with ketamine administered for either induction or maintenance in 149 procedures (78%) [76]. Pulmonary hypertension was mild in 23%, moderate in 37%, and severe in 40%. There were nine major complications, including three cardiac arrests (1.7% incidence) and 20 minor complications; the majority of minor complications were self-limiting arrhythmias and hypotension. Ketamine administration was not associated with any of these complications, whether administered as the sole anesthetic agent or combined with volatile agents or propofol. The authors conclude that ketamine appears to be a safe anesthetic option for children with pulmonary hypertension.

Ketamine, supplemented with small doses of midazolam and/or morphine, has been used for interventional cardiac catheterization procedures [77] and for postoperative analgesia after cardiac surgery in children. Hemodynamic stability has been excellent, with few complications. The most notable adverse effect was transient apnea in 10% of spontaneously breathing newborns undergoing balloon atrial septostomy in the catheterization laboratory.

There is limited information regarding the effect of ketamine on electrophysiologic study parameters. Char et al. reported on 22 children aged 5–17 years undergoing electrophysiologic study and ablation for SVT who had a baseline propofol infusion for sedation [78]. Dexametomidine loading dose 1 µg/kg followed by infusion of 0.7 µg/kg/hour was initiated, and electrophysiologic parameters measured. Then, with dexametomidine still infusing, a ketamine load of 1 mg/kg followed by infusion of 1 mg/kg/hour was given, and parameters again measured. Dexametomidine depressed sinus node function (sinus node recovery time), prolonged QT interval, and increased AV node refractory period. All of the abnormal parameters were returned completely or partially to baseline values after ketamine. Atiyeh et al. reported on a 21-year-old female undergoing electrophysiologic study for refractory paroxysmal idiopathic ventricular tachycardia (VT) [79]. Anesthesia maintenance consisted of low-dose propofol, alfentanil, and sevoflurane, and VT could not be induced despite isoproterenol infusion being increased to 5 µg/kg/min. After initiation of ketamine 15 µg/kg/min, VT could be easily and reproducibly induced, allowing successful mapping an ablation of VT focus.

Intramuscular induction of anesthesia may be achieved with ketamine 5 mg/kg, succinylcholine 4 mg/kg, and atropine 20 µg/kg mixed in the same syringe. This regimen is useful for small patients who present to the OR without IV access in whom the inhalational induction of anesthesia may produce undesirable hemodynamic effects. Endotracheal intubation can usually be achieved in 3–5 minutes, and attention can be turned to establishing IV access with the airway secure and a stable hemodynamic state. Ketamine may also be employed as a premedication, with an oral dose of 5–6 mg/kg most commonly administered.

In summary, ketamine is an attractive choice for IV or IM induction of anesthesia in patients with CHD with good or moderately limited hemodynamic reserve, including those with pulmonary hypertension or cyanosis. However, care must be taken in patients with severely limited cardiac reserve and depressed myocardial contractility. Such patients may be chronically receiving β-adrenergic or similar agents, or their own endogenous sympathomimetic system might be maximally stimulated because of a low CO state. The myocardial depressant properties of ketamine may be unmasked and lead to hemodynamic compromise.
KEY POINTS: KETAMINE

- Ketamine will increase HR and blood pressure, and preserve or increase myocardial contractility in patients with good hemodynamic reserve.
- Ketamine may act as a direct myocardial depressant in patients with poor ventricular function whose myocardial $\beta$-adrenergic receptors are downregulated from endogenous or exogenous catecholamines.
- Ketamine is a safe anesthetic in pulmonary hypertension if oxygenation and ventilation are maintained.

Etomidate

Etomidate is an imidazole derivative introduced into clinical practice in 1972. It is thought to produce its hypnotic effects (without analgesia) by interaction with gamma-aminobutyric acid receptors [65]. Besides having a desirable lack of effect on hemodynamics, etomidate reduces cerebral blood flow and cerebral metabolic rate for oxygen consumption (30–50%), and intracranial pressure. It has little effect on ventilation, does not release histamine, and does not change airway smooth muscle tone. Of all of the available IV induction agents, etomidate consistently demonstrates the least direct myocardial depression in several in vitro models. Two well-designed studies using adult human atrial and ventricular tissue demonstrated no effect of etomidate on myocardial contractility in concentrations seen in clinical use (Figure 6.8). In the same model, ketamine showed slight, and thiopental strong, negative inotropic effects in clinical concentration ranges. This was true even in abnormal myocardial samples of ventricular tissue taken from hearts removed for cardiac transplantation [52,80]. In a study of right ventricular

Figure 6.7 Pulmonary vascular resistance changes in 15 children with pulmonary hypertension undergoing cardiac catheterization, in response to ketamine 2 mg/kg intravenously, followed by an infusion of 10 $\mu$g/kg/min while breathing spontaneously with a baseline of 0.5 MAC sevoflurane. T1, baseline before ketamine; T2, 5 minutes after ketamine load; T3, 10 minutes after ketamine load; and T4, 15 minutes after ketamine load. (Source: Williams et al. [75]. Reproduced with permission of Lippincott Williams & Wilkins.)

Figure 6.8 Developed tension over time ($\Delta$T/Δt) in cardiac muscle trabeculae in explanted hearts from adults undergoing cardiac transplantation in response to increasing etomidate concentrations. The upper limit of clinical concentration is 4 $\mu$M. A, atrial muscle; V, ventricular muscle; vehicle, 35% propylene glycol, in which etomidate is solubilized. * P < 0.05 versus A-vehicle control; ¶ P < 0.05 versus V-vehicle control, and § P < 0.05 versus preceding dose. Numbers in parentheses represent numbers of muscle strips/number of patients. Iso, change with addition of 1 $\mu$M isoproterenol. (Source: Sprung et al., 2000. Reproduced with permission of Lippincott Williams & Wilkins.)
tissue excised from infants and children during TOF repair, etomidate did not change contractility in the clinical concentration range in an *in vitro* tissue bath study, but did blunt responsiveness to isoproterenol at high concentrations, raising the possibility that the pediatric myocardium may respond differently after etomidate [81].

All of these beneficial effects of etomidate are offset by a number of undesirable effects. Etomidate is water-insoluble and is thus formulated in propylene glycol, commonly producing pain on injection, which may be ameliorated by pretreatment with lidocaine and 1:1 dilution with sterile water. A new etomidate formulation dissolving the drug in a fat emulsion of medium and long-chain triglycerides virtually eliminates pain on injection in children [82]. Myoclonic movement, hiccoughs, and nausea and vomiting are frequent [65]. It should be noted that, as in adults, a single dose of etomidate used for induction in pediatric patients undergoing cardiac surgery with CPB suppresses the usual increase in plasma cortisol levels by inhibiting 11ß-hydroxylase, the enzyme that converts 11-deoxycortisol to cortisol [44]. Cortisol levels returned to normal 24 hours later. Two recent adult studies reported effects of etomidate induction on 30-day outcomes. Komatsu et al. reported on 2,144 ASA III and IV patients given etomidate for induction for non-cardiac surgery, propensity-matched with 5,233 given propofol [83]. Seventy-four percent of patients had cardiovascular disease, and those receiving etomidate had an odds ratio of 2.5 for death, 1.5 for cardiovascular morbidity and a longer hospital stay, but no difference in infectious morbidity or intraoperative vasopressor use. The authors speculate that adrenal suppression could have a bearing on this association. Wagner et al. reported a cohort of 3,127 adults undergoing cardiac surgery, 62% of whom received etomidate for induction [84]. No difference in severe hypotension, in-hospital mortality, mechanical ventilation time, or hospital length of stay was demonstrated either before or after propensity score analysis. They conclude that etomidate should remain an acceptable option in these patients.

There are a few published reports of the hemodynamic effects of etomidate in children with CHD. Twenty patients with a variety of congenital defects were studied in the cardiac catheterization laboratory. These authors found that etomidate at 0.3 mg/kg bolus followed by an infusion of 26 μg/kg/min had similar effects as ketamine 4 mg/kg followed by an infusion of 83 μg/kg/min, namely a slight increase in HR but no change in MAP during induction or the 60-minute infusion [85]. Sarkhār et al. [86] studied etomidate bolus 0.3 mg/kg in 12 children undergoing cardiac catheterization for device closure of ASD, or radiofrequency ablation of atrial arrhythmias. There were no significant changes in any hemodynamic parameter, including HR, MAP, filling pressures, vascular resistances, Qp:Qs, or mixed venous oxygen saturation. Dhawan et al. studied 30 children under 12 years old undergoing cardiac catheterization with FiO2 0.21 and basal sedation with morphine and midazolam, who had direct hemodynamic measurements before and after a 0.3 mg/kg bolus of etomidate [87]. In 15 patients with right-to-left shunt (TOF, VSD/pulmonic stenosis), there was no change in HR, right atrial pressure, MAP, Qp:Qs, or arterial blood gas values. In 15 patients with left-to-right shunts (VSD, ASD, PDA, aortopulmonary window), all of whom had significant baseline pulmonary hypertension, there was also no change in HR, right atrial pressure, mean pulmonary artery pressure (69 mmHg before, 71 mmHg after), Qp:Qs, PVR index (PVRI), or SVR index (SVRI).

A case report of stable hemodynamics in a pediatric patient with end-stage cardiomyopathy receiving a second anesthetic 4 weeks after cardiovascular collapse with ketamine induction (see earlier) demonstrates the utility of etomidate in this population [68]. Etomidate has been utilized for induction of anesthesia in adults with congenital cardiac conditions such as ruptured aneurysm of the sinus of Valsalva, and cesarean section in a patient with uncorrected coronary artery to pulmonary artery fistula, and was demonstrated to be devoid of cardiovascular effects in these patients [88,89].

Thus it would appear that etomidate is best utilized in patients with the most limited cardiac reserve. It seems to be particularly useful in teenagers or adults with poorly compensated palliated CHD presenting for cardiac transplantation, or revision of previous surgeries. Adrenal suppression occurs with even a single dose of etomidate, and consideration should be given to administer additional supplemental corticosteroids in patients receiving corticosteroids or at risk of prolonged adrenal suppression. Many patients receiving etomidate for induction will already be receiving corticosteroids as part of their regimen for transplant or cardiac surgery. Repeated or prolonged administration of etomidate is not recommended for this reason.

### Key Points: Etomidate

- Etomidate has no direct myocardial depressant effect at clinically administered doses, and as such is a preferred induction agent for patients with poor ventricular function.
- Etomidate has no effect on systemic or pulmonary hemodynamics when administered to patients with intracardiac shunting, including those with pulmonary hypertension.
- Etomidate will suppress adrenal function with a single induction dose.

### Dexmedetomidine

Dexmedetomidine was introduced in the US in 1999 as a sedative agent for mechanically ventilated adults in intensive care settings. It is an IV agent that is an imidazole derivative, and a highly selective α2-adrenergic
receptor agonist (1620:1 $\alpha_2$ to $\alpha_\text{IR}$ activity, vs. 220:1 for clonidine). Dexmedetomidine is a centrally acting agent with $\alpha_2$-receptor binding sites in the locus ceruleus in the brain which produces sedation, and $\alpha_2$ receptors in the spinal cord, which produce some analgesic effect. Dexmedetomidine loading doses, particularly large doses of 0.75–1 $\mu$g/kg administered rapidly over <10 minutes, usually cause systemic hypertension with binding to peripheral arterial $\alpha_2$ receptors [90]. With a continuous infusion, dexmedetomidine causes a dose-dependent decrease in HR and MAP by decreasing CNS sympathetic nervous system activity. It also potentiates opioid effects and is thus potentially suitable for use both during and after pediatric cardiac surgery, as a component of a general anesthetic and as a sedative/analgesic agent in the intensive care unit (ICU). The usual dose for sedation is 0.2–0.7 $\mu$g/kg/hour; a loading dose of 0.5–1 $\mu$g/kg given over 10 minutes can be utilized if desired. It has minimal effect on respiration, and its clearance of 13 mL/kg/min, volume of distribution of 1.0 L/kg, and terminal half-life of 1.8 hours in children without heart disease are similar to adult values [91]. In infants aged 1–24 months receiving dexmedetomidine sedation after congenital heart surgery with bypass, clearance using allometric scaling was 28 mL/kg/min$^{0.75}$, and central volume of distribution was 1.2 L/kg [92]. In both premature infants and full-term neonates <30 days of age undergoing congenital heart surgery, dexmedetomidine clearance is substantially reduced and elimination half-life is substantially increased to as high as 7.6 hours for preterms. Both values assume near-adult levels after about 44 weeks postconceptional age [93,94]. Because it is an imidazole derivative structurally similar to etomidate, dexmedetomidine theoretically has the potential for adrenal suppression with prolonged use. Venn et al. reported no difference in cortisol, adrenocorticotropic hormone (ACTH), growth hormone, prolactin, insulin, glucagon, and interleukin-6 in 20 adult ICU patients randomized to received propofol or dexmedetomidine [95]. There were also no differences between groups in response to ACTH stimulation test. However, Tucker et al. described a 1-year-old 10 kg burn patient who received high-dose dexmedetomidine infusion for 7 days, who developed hypotension with low baseline cortisol levels and inadequate response to ACTH stimulation test, indicating adrenal insufficiency, which they believed was possibly related to dexmedetomidine [96]. No additional published reports exist implicating dexmedetomidine in adrenal suppression.

Dexmedetomidine has been studied as an adjunct agent in general anesthesia for pediatric cardiac surgery. In a study by Muktar et al., dexmedetomidine 0.5 $\mu$g/kg load followed by 0.5 $\mu$g/kg/hour infusion, with an isoflurane–fentanyl–midazolam anesthetic, significantly reduced HR, MAP, cortisol, blood glucose, and serum catecholamine response in children aged 1–6 years undergoing cardiac surgery with bypass, when compared with the baseline anesthetic [97].

Dexmedetomidine has been studied for postoperative sedation after pediatric cardiac surgery. Chrysostomou et al. studied 38 pediatric patients of median age 8 years after two-ventricle repair with CPB. Thirty-three of 38 patients had tracheal extubation in the OR. Dexmedetomidine infusion rate varied from 0.1 to 0.75 $\mu$g/kg/hour (mean 0.3), and the desired sedation was achieved in 93% of patients, and analgesia in 83% of patients. There was no respiratory depression, but hypotension was observed in 15% of patients [98]. Dexmedetomidine has also been described as useful in weaning opioid-tolerant cardiac surgery patients relatively quickly with no hemodynamic side-effects [99]. Dexmedetomidine as a sole sedative agent for pediatric cardiac catheterization was studied by Munro et al. in 20 children [100]. A loading dose of 1 $\mu$g/kg was followed by an infusion of 1 $\mu$g/kg/hour, and propofol boluses were given for movement or increasing bispectral index value. Sixty percent of patients required propofol boluses, and there was a slight decrease in MAP but not in HR, and no patient experienced airway obstruction or respiratory depression. Dexmedetomine plus ketamine has been compared with dexmedetomidine plus propofol for pediatric cardiac catheterization in 44 patients [101]. There was no difference in sedation scores or respiratory parameters: HR was slower in the dexmedetomidine group, while MAP was not different. Recovery time was significantly longer in the dexmedetomidine group than in the propofol group.

It is important to note that dexmedetomine frequently causes bradycardia and thus may not be suitable as a sedative for electrophysiologic studies. In 12 children undergoing electrophysiologic studies, Hammer et al. found that dexmedetomidine 1 $\mu$g/kg load followed by 0.7 $\mu$g/kg/hour infusion for 20 minutes decreased HR by 15–20%, but more importantly depressed sinus node recovery times, sinus node automaticity, and increased AV nodal block cycle lengths and PR interval [102] (Table 6.2).

In more recent studies, case series reporting dexmedetomidine administration for intraoperative and postoperative use have been described in a variety of congenital and acquired heart diseases, including those with critical heart disease and decreased ventricular function. Klampf et al. prospectively randomized 32 children undergoing two-ventricle cardiac repairs to a midazolam–fentanyl anesthetic or a dexmedetomine–fentanyl anesthetic [103]. Dexmedetomidine was infused at 1.0 $\mu$g/kg/hour without loading dose for the first hour, and then decreased to 0.5 $\mu$g/kg/hour, and HR and BP were recorded. Isoflurane was used to supplement the anesthetic and to control hemodynamic variables. HR and BP decreased from baseline in both groups, but increased after skin incision only in the midazolam–fentanyl group. Eighty-six percent of the midazolam–fentanyl group required supplemental isoflurane, as compared with 31% of the dexmedetomidine–fentanyl group. In the dexmedetomidine group, two patients required phenylephrine before bypass for hypotension and one required atropine for bradycardia.
Electrophysiologic variables at baseline and after a 20-minute infusion of dexmedetomidine

<table>
<thead>
<tr>
<th>Table 6.2</th>
<th>Electrocardiogram variables at baseline and after a 20-minute infusion of dexmedetomidine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
</tr>
<tr>
<td><strong>Surface ECG intervals</strong></td>
<td></td>
</tr>
<tr>
<td>SCL</td>
<td>606 ± 140 ms</td>
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<tr>
<td>PR</td>
<td>144 ± 19 ms</td>
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<tr>
<td>QRS</td>
<td>76 ± 11 ms</td>
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<tr>
<td>QTc</td>
<td>394 ± 9 ms</td>
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<tr>
<td><strong>Sinus automaticity</strong></td>
<td></td>
</tr>
<tr>
<td>CSNRT</td>
<td>212 ± 179 ms</td>
</tr>
<tr>
<td><strong>Atrial muscle properties</strong></td>
<td></td>
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<tr>
<td>AERP</td>
<td>207 ± 31 ms</td>
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<tr>
<td>AV nodal properties</td>
<td></td>
</tr>
<tr>
<td>AH interval</td>
<td>73 ± 14 ms</td>
</tr>
<tr>
<td>AVNBCL</td>
<td>352 ± 87 ms</td>
</tr>
<tr>
<td>AVNERP</td>
<td>310 ± 85 ms</td>
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<tr>
<td>VABCL</td>
<td>372 ± 111 ms</td>
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<tr>
<td>His Purkinje properties</td>
<td></td>
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<tr>
<td>HV interval</td>
<td>40 ± 7 ms</td>
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<tr>
<td>Ventricular muscle properties</td>
<td></td>
</tr>
<tr>
<td>VERP</td>
<td>220 ± 22 ms</td>
</tr>
</tbody>
</table>

ECG, electrocardiogram; SCL, sinus cycle length; PR, PR interval; QRS, QRS duration; QTc, corrected QT interval; CSNRT, corrected sinus node recovery time; AERP, atrial effective refractory period; AH interval, atrial–His interval; AVNBCL, AV node block cycle length; AVNERP, AV node effective refractory period; VABCL, ventriculoatrial block cycle length; HV interval, His–ventricular interval; VERP, ventricular effective refractory period.

Source: Hammer et al. [102]. Reproduced with permission of Lippincott Williams & Wilkins.

In a retrospective review, Lam et al. described 50 neonates and infants ≤ 12 months receiving dexmedetomidine sedation for a median of 78 hours, at doses ranging from 0.1 to 1.5 μg/kg/hour after congenital heart surgery or cardiac transplantation [104]. Despite a significant decrease in HR and MAP as well as central venous pressure after initiation of the dexmedetomidine infusion, inotrope score progressively decreased, and no critical hemodynamic events or bradycarrythmias were observed that required boluses of IV fluids, adrenergic agents or atropine, or escalation of inotropic support. The authors concluded that dexmedetomidine is safe from a hemodynamic standpoint and can reduce opioid and benzodiazepine dosing. Lam et al. also described dexmedetomidine use in 21 infants (median age 3–4 months, and weight 4.7–6.6 kg) with congestive heart failure as part of a sedation regimen for intensive care, and compared safety and efficacy with 23 patients with congestive heart failure who were sedated without dexmedetomidine [105]. All patients were awaiting orthotopic heart transplantation and were studied in the 18 days before transplant; 75% had dilated cardiomyopathy and all but one was receiving mechanical ventilation.

Mean arterial pressures were lower in the first 24 hours in the dexmedetomidine group, and HR was lower in the dexmedetomidine group in the first 6 hours. Three patients in the dexmedetomidine group (14%) had greater than a 50% decrease in MAP in the first 3 hours after dexmedetomidine infusion initiated at 0.5–0.6 μg/kg/hour; one of the three also had bradycardia to 48 beats/minute. Opioid and benzodiazepine doses were significantly lower in children receiving dexmedetomidine. The authors concluded that dexmedetomidine administration in infants with heart failure appears to be generally safe, but should be used cautiously.

Su et al. studied dose response of dexmedetomidine as a primary sedative in a dose escalation study of 36 infants aged 1–24 months after cardiac surgery, with loading dose and infusion rates spanning the range of doses used clinically [106]. Heart rates for the entire group decreased from a mean of 161 beats/minute at baseline to a mean of 132 beats/minute during dexmedetomidine infusion (P < 0.0001). The decrease in HR was dose- and plasma level-dependent with larger decreases in higher-dose groups. MAP and inotrope infusion scores did not change significantly during infusion. A single patient in the intermediate dosing cohort experienced intermittent complete heart block 5 hours after dexmedetomidine infusion initiation, resulting in bradycardia, which did not recur following discontinuation.

Dexmedetomidine is often cited as facilitating early tracheal extubation because of its minimal effects on respiration and ability to reduce opioid doses. Le et al. reported a retrospective review of 269 patients undergoing cardiac surgery, 89 of whom received dexmedetomidine for postoperative sedation, and 180 matched controls from the year before introduction of dexmedetomidine to their institution in 2007 [107]. There were no differences in any ventilation parameter: 42% of both groups had tracheal extubation in the OR; 75% of controls and 76% of dexmedetomidine patients were extubated in the first 24 hours, and the mean ventilator time was 29 hours in the control group and 35 hours in the dexmedetomidine group (P = 0.17), with no differences in patients <12 months. The authors concluded that dexmedetomidine did not have a significant impact on early extubation.

The effect of dexmedetomidine on pulmonary artery pressure and resistance has been reported in several recent studies. Lazol et al. studied 22 patients (median age 11 months) after reparative two-ventricle cardiac surgery, who received a dexmedetomidine loading dose (median 0.62 μg/kg) and infusion (median 0.5–0.65 μg/kg/hour) and had echocardiographic estimation of pulmonary artery pressure using tricuspid regurgitation jet velocity [108]. Median pulmonary artery systolic pressure decreased from 30 mmHg before dexmedetomidine to 24 mmHg at 6 minutes after the loading dose, and 26 mmHg at 1 hour (P < 0.001). The ratio of pulmonary to systemic systolic pressure decreased from 33% to 25% (P = 0.002). There were no changes in inotropic infusions or left ventricular contractility. Freisen et al. studied 42
patients undergoing cardiac catheterization, 21 for routine post-transplant surveillance, and 21 for pulmonary hypertension studies [109]. After sevoflurane induction, endotracheal anesthesia was maintained with midazolam and remifentanil, and the response to dexmedetomidine loading doses of 0.5, 0.75, or 1.0 μg/kg over 10 minutes was measured. Most hemodynamic responses were similar in both groups, with a significant decrease in HR and an increase in SVRI. Cardiac index did not change, but there was a small, statistically significant increase in pulmonary artery pressure in transplant patients but not in those with pulmonary hypertension. Changes in PVRI and PVRI/SVRI were not significant in either group.

Finally, dexmedetomidine has been demonstrated in several case series to decrease the incidence of postoperative ventricular and supraventricular tachydysrhythmias in infants and children after congenital heart surgery with bypass [110].

Dexmedetomidine is a potentially useful agent as an adjunct to general anesthesia, a postoperative sedative, and an adjunct sedative for cardiac catheterization (non-electrophysiologic studies) in pediatric patients with CHD. The patient must be able to tolerate the predictable decrease in HR, and frequent decrease in MAP associated with dexmedetomidine infusion. Clearance of dexmedetomidine is reduced in neonates, necessitating lower doses in this age group and heightened monitoring for side-effects.

The presence of a right-to-left intracardiac shunt decreases the rate of rise of the concentration of inhaled anesthetic in the arterial blood, as a portion of the systemic CO bypasses the lungs and then dilutes the anesthetic concentration in the systemic arterial blood [111]. The anesthetic concentration in the blood thus never equals the exhaled concentration. Huntington et al. [111] studied six children with right-to-left shunts from a fenestrated Fontan operation whose average pulmonary to systemic blood flow ratio was 0.58. These patients achieved an arterial anesthetic concentration (Fa) of only 55% of inspired halothane concentration (Fi) after 15 minutes during wash-in of 0.8% halothane. After closure of the right-to-left shunt (occlusion of Fontan fenestration in the cardiac catheterization laboratory), the arterial concentration of halothane was equal to the inspired concentration. This difference between Fa and Fi is greater during induction or washout; and greater with less soluble drugs, such as sevoflurane, desflurane, and N2O, than with more soluble drugs, such as halothane. Conversely, if blood concentration of a volatile agent is high, the rate of decrease during washout is slowed with right-to-left shunting. This is an important consideration if myocardial depression occurs, and the usual approach to reduce or discontinue the volatile agent and increase minute ventilation is often ineffective in this situation.

In the face of significant right-to-left intracardiac shunting, IV agents given by bolus may pass directly into the left side of the heart with less dilution by systemic venous blood and passage through the pulmonary vascular system. This may result in transient high arterial, brain, and cardiac concentrations of drugs such as lidocaine [112]. Intravenous induction agents and muscle relaxants may also achieve sufficient arterial and brain concentrations more rapidly with right-to-left intracardiac shunts [113].

Left-to-right intracardiac shunts have little effect on the speed of induction with inhaled anesthetic agents [114]. The recirculation of blood through the lungs results in increased uptake of anesthetic and in a higher blood anesthetic concentration in the pulmonary capillaries, which reduces the concentration gradient between the alveoli and the pulmonary capillary blood, reducing anesthetic uptake. The two effects cancel each other. Only in the case of severe congestive heart failure from left-to-right shunt, with significant interstitial and alveolar edema, would left-to-right intracardiac shunting be expected to slow inhalation induction from the combined effects of diffusion limitation and ventilation-perfusion mismatch, resulting in alveolar dead-space ventilation in which no new anesthetic agent is taken up.

**Cardiopulmonary bypass**

The onset of CPB affects plasma levels of IV drugs by a number of different mechanisms [115]. Hemodilution of the patient’s blood volume by a factor of 50–300%, depending on the size of the patient and the priming volume of the circuit, causes an immediate reduction in plasma levels. Many drugs also bind to the membrane oxygenator and other components of the bypass circuit, resulting in a further decrease in plasma levels. This effect

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**KEY POINTS: DEXMEDETOMIDINE**

- Dexmedetomidine reduces doses of opioids and benzodiazepines and may be a useful adjunct to intraoperative general anesthesia, and as a component of postoperative sedation regimens.
- Dexmedetomine bolus in larger doses results in hypertension; side-effects of infusions include hypotension and bradycardia.
- Dexmedetomidine affects cardiac conduction and may suppress supraventricular and ventricular arrhythmias, but sinus and junctional bradycardia and sinus arrest are unusual but potentially serious side-effects.

The major hemodynamic and cardiac rhythm effects of the anesthetics, sedatives, and analgesics discussed in preceding sections are presented in Table 6.3.

**Special conditions affecting anesthetic pharmacokinetics and pharmacodynamics in congenital cardiac anesthesia**

**Intracardiac shunts**

The presence of a right-to-left intracardiac shunt decreases the rate of rise of the concentration of inhaled anesthetic in the arterial blood, as a portion of the systemic CO bypasses the lungs and then dilutes the anesthetic concentration in the systemic arterial blood [111]. The anesthetic concentration in the blood thus never equals the exhaled concentration. Huntington et al. [111] studied six children with right-to-left shunts from a fenestrated Fontan operation whose average pulmonary to systemic blood flow ratio was 0.58. These patients achieved an arterial anesthetic concentration (Fa) of only 55% of inspired halothane concentration (Fi) after 15 minutes during wash-in of 0.8% halothane. After closure of the right-to-left shunt (occlusion of Fontan fenestration in the cardiac catheterization laboratory), the arterial concentration of halothane was equal to the inspired concentration. This difference between Fa and Fi is greater during induction or washout; and greater with less soluble drugs, such as sevoflurane, desflurane, and N2O, than with more soluble drugs, such as halothane. Conversely, if blood concentration of a volatile agent is high, the rate of decrease during washout is slowed with right-to-left shunting. This is an important consideration if myocardial depression occurs, and the usual approach to reduce or discontinue the volatile agent and increase minute ventilation is often ineffective in this situation.

In the face of significant right-to-left intracardiac shunting, IV agents given by bolus may pass directly into the left side of the heart with less dilution by systemic venous blood and passage through the pulmonary vascular system. This may result in transient high arterial, brain, and cardiac concentrations of drugs such as lidocaine [112]. Intravenous induction agents and muscle relaxants may also achieve sufficient arterial and brain concentrations more rapidly with right-to-left intracardiac shunts [113].

Left-to-right intracardiac shunts have little effect on the speed of induction with inhaled anesthetic agents [114]. The recirculation of blood through the lungs results in increased uptake of anesthetic and in a higher blood anesthetic concentration in the pulmonary capillaries, which reduces the concentration gradient between the alveoli and the pulmonary capillary blood, reducing anesthetic uptake. The two effects cancel each other. Only in the case of severe congestive heart failure from left-to-right shunt, with significant interstitial and alveolar edema, would left-to-right intracardiac shunting be expected to slow inhalation induction from the combined effects of diffusion limitation and ventilation-perfusion mismatch, resulting in alveolar dead-space ventilation in which no new anesthetic agent is taken up.

**Cardiopulmonary bypass**

The onset of CPB affects plasma levels of IV drugs by a number of different mechanisms [115]. Hemodilution of the patient’s blood volume by a factor of 50–300%, depending on the size of the patient and the priming volume of the circuit, causes an immediate reduction in plasma levels. Many drugs also bind to the membrane oxygenator and other components of the bypass circuit, resulting in a further decrease in plasma levels. This effect
<table>
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<td>NC Preserves myocardial contractility to 1.5 MAC in CHD</td>
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<td>++ with bolus; – – with infusion</td>
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MAP, mean arterial pressure; SVR, systemic vascular resistance; PAP, pulmonary artery pressure; +, small increase; ++, moderate increase; ++++, large increase; –, small decrease; – –, moderate decrease; – – –, large decrease; NC, no change; MAC, minimum alveolar concentration; CHD, congenital heart disease; α₂, alpha-2-adrenergic receptor.
is variable, and is dependent on the drug and its size and lipid solubility (octanol:water partition coefficient), the type of bypass circuit used (i.e., silicone vs. polypropylene), the age and size of the patient, and the plasma and bypass prime albumin concentrations. Hypothermia slows the metabolism of all drugs by reducing the rate of reaction of all enzymes involved in drug metabolism, whether they are in the liver (cytochrome P450 system), kidney, or plasma. Rewarming significantly increases the rate of metabolism of IV agents.

A constant, stable fentanyl plasma level [116] can be achieved in most children through the administration of a loading dose of 30–50 μg/kg followed by an infusion of 0.15–0.3 μg/kg/min. Plasma fentanyl levels decrease by 70–75% immediately upon institution of CPB with a silicone membrane oxygenator, presumably due to binding of the drug to oxygenator and bypass tubing. After cooling to 18–25°C, fentanyl metabolism decreases considerably and free drug concentrations change very little, even without added drug [117]. Metabolism then increases and drug levels decline in the plasma as rewarming proceeds. Data concerning common anesthetic adjuvants such as midazolam suggest similar changes in plasma concentrations [115]. Thus, without supplementation of IV agents such as fentanyl and midazolam, either just before or at the initiation of bypass, plasma levels of IV anesthetics will decline significantly and there is an increased risk of inadequate anesthesia. A similar risk would appear to be true during the final phases of the rewarming period. Indeed, this concept is borne out by recent studies using bispectral index as an indicator of depth of sedation in children undergoing bypass with mild hypothermia [118]. Modified ultrafiltration has been reported to double the plasma fentanyl concentrations in a study of five neonates and infants, from 12.4 to 27.5 ng/mL, presumably due to hemoconcentration [119].

Volatile agents may be used during bypass to supplement anesthetic depth, or as vasodilators. Isoflurane is most commonly utilized at a concentration of 0.5–2% inspired into the sweep gas of the bypass circuit. Multiple adult studies have demonstrated the effectiveness and relatively rapid wash-in of this agent [115]. The blood levels of isoflurane are highly dependent on the type of oxygenator used. Wiesenack et al. reported on isoflurane blood and oxygenator concentrations in 24 adults undergoing elective coronary bypass surgery [120] (Figure 6.9). Isoflurane (1%) was added to the CPB sweep gas, at 3 L/min flows for 15 minutes, and isoflurane concentrations were measured in the blood, and at the oxygenator gas outflow port. Microporous polypropylene (PPL) hollow-fiber membrane oxygenators were compared with plasma-tight poly-(4-methyl-1-pentene) (PMP) membrane oxygenators, and dramatic differences were found. The PPL oxygenator had an area under the curve of blood level of isoflurane 8.5–13 times higher than PMP oxygenators, with almost no blood transfer of isoflurane with PMP models. Isoflurane concentration was also significantly lower at the oxygenator exhaust port with the PMP models, reaching only 60% of inspired levels at 15 minutes, whereas with the PPL models exhaled isoflurane was equal to inspired after less than 5 minutes. Most CPB oxygenators in clinical pediatric use are PPL models. Pediatric in vitro or in vivo data have not been published, and because sweep gas flow rates are often less than 1 L/min in small infants, volatile anesthetic uptake is probably much slower and it cannot be assumed that the desired blood anesthetic level is rapidly reached when volatile anesthetic agents are administered through the bypass circuit to infants and small children. In this study, blood levels were continuing to increase after 15 minutes. Washout of volatile agents is also slower at low sweep gas rates, and volatile agents should be discontinued early during the rewarming period to avoid the potential myocardial depressant effects of these agents while attempting to wean the patient from bypass.

Neuromuscular blocking agents have an enhanced effect during hypothermic bypass, [115] both from decreased metabolism and clearance, and because of the effects of hypothermia to potentiate the pharmacodynamic effects of the drugs at the neuromuscular junction. These effects rapidly reverse themselves during rewarming. These drugs have a small volume of distribution and thus few tissue stores from which to re-equilibrate plasma levels. Thus, plasma levels would be expected to decline in proportion to the hemodilution factor of the pump prime, subject to changes in protein binding. This may be offset by reductions in the patient’s plasma volume on bypass due to vasoconstriction. The action of these drugs in response to bypass is accordingly more variable than other commonly used IV anesthetic agents. There is limited pediatric information available. Monitoring of neuromuscular blockade with a twitch monitor is recommended if early reversal is desired.

**Hypothermia**

Studies performed on animal models reveal hypothermia reduces the MAC of volatile anesthetics [121]. Liu et al. [122] studied the MAC of isoflurane in 33 children with left-to-right intracardiac shunts at 37°C, 34°C, or 31°C. They found that MAC was reduced by 28% at 31°C when compared with normothermia, indicating a decrease in MAC of approximately 5% per °C cooling. The bispectral index value correlates strongly with temperature during mild hypothermic bypass in children [123], offering supporting evidence that hypothermia alone provides general anesthesia.

**KEY POINTS: SPECIAL CONDITIONS AFFECTING ANESTHETICS**

- Right-to-left intracardiac shunting slows volatile anesthetic uptake and washout; the greatest effect is in less soluble agents such as sevoflurane and desflurane, while the effect is smaller with the more soluble agents, such as halothane.
Figure 6.9 Isoflurane blood concentrations ($C_{\text{isoflurane}}$ [μM]) for the uptake and elimination sequence for two different oxygenators; each line represents a single patient. (A) CapioxRX25 PPL oxygenator. (B) Oxygenator exhaust port isoflurane ($F_{\text{E}}$) for uptake and elimination sequence for the four oxygenators. (C) Quadrox D PMP oxygenator. Values are median (range). *, $P < 0.01$ vs. Quadrox$^{D}$; **, $P < 0.01$ vs. Hilite 7000LT®. Polypropylene (PPL) oxygenators (CapioxRX25, Hilite 7000) had greater transfer of isoflurane across membrane oxygenator and into blood than polymethylpentane (PMP) oxygenators (Quadrox$^{D}$, Hilite 7000LT). (Source: Wiesenack et al. [121]. Reproduced with permission of Lippincott Williams & Wilkins.)

- CPB has highly variable effects on anesthetic drug pharmacokinetics and pharmacodynamics, depending on the type of oxygenator, flows, temperatures, and ultrafiltration.
- Hypothermia significantly decreases anesthetic requirements by lowering MAC and slowing metabolism of IV drugs.

### Neuromuscular blocking agents and antagonists

#### Succinylcholine

Succinylcholine is rarely indicated for anesthesia for CHD because of its association with the development of malignant hyperthermia, hyperkalemic cardiac arrest, and bradycardia after IV bolus administration. Succinylcholine will produce a more rapid onset of muscle relaxation than non-depolarizing muscle relaxants, [124] and generally its use is limited to full-stomach emergency indications, i.e., cardiac transplant, to treat laryngospasm, and as a component of an intramuscular induction.

Infants and children frequently exhibit bradycardia, junctional rhythm, ventricular premature beats and, rarely, asystole, after IV dosing of succinylcholine 1–2 mg/kg without atropine pretreatment. The frequency of all of these arrhythmias increases with a second dose. A dose of 4 mg/kg given IM, either alone or with atropine 20 μg/kg, and ketamine 5–10 mg/kg in the same syringe rarely causes bradycardia [125].

#### Pancuronium

Pancuronium is frequently used in doses of 0.1–0.3 mg/kg for initial relaxation for CHD [126] and is particularly
desirable in many small infants and young children because of the vagolytic and mild sympathomimetic effects, which preserve or increase HR, especially in the face of concomitant bradycardia from high-dose opioid anesthesia. In recent years, this drug has become unavailable in many parts of the world.

**Vecuronium**

Vecuronium is devoid of cardiovascular effects in children [127]. It is a useful agent when increases in HR are undesirable (e.g., in hypertrophic cardiomyopathy). When no uncertainties about ability to manage the airway are evident, it is a useful alternative to succinylcholine in a dose of 0.3–0.4 mg/kg for modified rapid sequence induction.

**Rocuronium**

Rocuronium is a moderately rapid-onset, intermediate-duration, non-depolarizing neuromuscular blocker that is useful at a dose of 0.6–1.2 mg/kg IV. At the upper dose ranges it is an acceptable substitute for succinylcholine for modified rapid sequence induction. Cardiovascular effects are minimal, but because it causes pain on injection, or because it is a weak vagolytic medication, an increase in HR is often observed after injection. This agent may be utilized for IM administration in doses of 1.8–2 mg/kg, and when injected into the deltoid muscle will produce suitable intubating conditions in 3–4 minutes [128].

**Atracurium and cisatracurium**

Atracurium and cisatracurium are non-organ-dependent for elimination and are attractive choices in the face of significant hepatic and renal dysfunction. Atracurium at high dosages frequently causes histamine release, resulting in hypotension when injected rapidly [124], making it undesirable for many patients with CHD. Cisatracurium is a stereoisomer of atracurium, also degraded by Hoffmann elimination, does not release histamine, and like vecuronium is devoid of cardiovascular effects even when administered rapidly [129].

**Antagonists**

The muscarinic effects of neostigmine must be blocked by atropine or glycopyrrolate to prevent potentially serious decreases in HR. Because the onset of cardiovascular effects of neostigmine and glycopyrrolate are similar, a most useful regimen is to utilize neostigmine and glycopyrrolate in the same syringe in a 5:1 ratio of neostigmine:glycopyrrolate (i.e., 75:15 μg/kg) injected slowly to minimize the small risk of arrhythmia with neostigmine. Despite longstanding use of neostigmine for reversal of neuromuscular blockade, it may cause bradycardia or cardiac arrest, even if administered with appropriate anticholinergic agents. Sawasdiwipachai et al. reported on a case of a 1-year-old who suffered a cardiac arrest 2 weeks after a heart transplant, after a myocardial biopsy, and reversal of cisatracurium neuromuscular blockade with 70 μg/kg neostigmine and glycopyrrolate 14 μg/kg [130]. Acute cardiac rejection and an abnormal conduction system were postulated as causes in this infant, with direct effect on the muscarinic receptors playing a role. Two additional cases of cardiac arrest in children with transplanted hearts have recently been reported [131]. The authors suggest preadministration of glycopyrrolate to avoid effects related to the muscarinic receptor, and considering sugammadex as an alternative with no effect on acetylcholine receptors, as reversal strategies in patients with transplanted hearts.

Sugammadex, a new agent which can reverse neuromuscular blockade by competitive displacement of non-depolarizing neuromuscular blocking agents from the acetylcholine receptor, has been reported to prolong QTc interval in some adult patients [132]. De Kam et al. administered sugammadex to 80 healthy adult volunteers in a randomized, double-blind, placebo-controlled study designed to assess its effect on QTc intervals [133]. Sugammadex doses up to 32 mg/kg were studied, with either rocuronium 1.2 mg/kg or vecuronium 0.1 mg/kg, with an active control drug known to prolong QTc intervals. No effect was detected on the QTc intervals up to 24 hours after administration of sugammadex. Finally, Cammu et al. studied 12 adult patients with heart failure and EF <25% undergoing general anesthesia with rocuronium neuromuscular blockade, and reversal with sugammadex 2 mg/kg [134]. Blood pressure and HR did not change for the first 10 minutes after administration, and both had increased by 30 minutes. Reversal of neuromuscular blockade was effective in all patients but, at 2.8 minutes, the mean time to reversal was longer than observed in healthy patients. No sugammadex-related adverse events were reported. To date, there have not been any published studies in pediatric patients with heart disease.

**Chapter 6 Anesthetic Agents and Their Cardiovascular Effects**

**KEY POINTS: NEUROMUSCULAR BLOCKING AGENTS AND ANTAGONISTS**

- Succinylcholine may cause bradycardia, junctional rhythm, ventricular premature beats, and asystole in patients with CHD.
- Vecuronium, rocuronium, and cisatracurium are generally devoid of cardiovascular effects.
- Neostigmine may cause bradycardia or sinus arrest; adequate doses of anticholinergic agents must be administered concomitantly.

**Selection of anesthetic regimen in CHD**

Pediatric patients with congenital and acquired heart disease are known to be at significantly higher risk for
cardiac arrest and death, and other major complications of anesthesia. The four highest risk groups appear to be patients with suprasystolic pulmonary hypertension, severe left ventricular outflow tract obstruction, significantly decreased ventricular function, and infants with a single functional ventricle and a systemic to pulmonary artery shunt [8,22,23,135–138]. The incidence of cardiac arrest related to anesthesia is reported to be 0.7–6% in these patient groups, and anesthetic agent selection plays a role in at least some of these adverse outcomes.

The ideal anesthetic regimen for CHD would be devoid of any undesirable hemodynamic effects, would produce analgesia, amnesia, and muscle relaxation, and be rapidly titratable. Hemodynamic perturbations would be controlled with vasoactive and inotropic agents alone, also rapidly titratable, achieving a desirable separation of anesthetic and hemodynamic effects for the two classes of drugs. The ideal regimen does not exist, and the pediatric cardiac anesthesiologist is left with devising an individualized strategy for each patient, accounting for pathophysiology and desired hemodynamic goals in each patient. Hemodynamic effects are continuously monitored, doses of different drugs are often titrated independently and at frequent intervals, and the anesthesiologist must sometimes change strategies. Vasoactive and inotropic agents must sometimes be added to counteract the untoward effects of a chosen anesthetic regimen.

The ideal anesthetic plan would involve thorough review of all data, including echocardiography and other imaging, careful examination of the patient, and the construction of a set of hemodynamic goals, which also consider the duration and invasiveness of the planned surgery, intervention, or diagnostic study. The well-known difficulties in approaching infants and young children with stranger anxiety and without IV access must frequently be taken into account. Then, an intelligent anesthetic regimen is selected which is likely to achieve those goals based on the known cardiovascular effects of the drugs as presented in this chapter. For example, the patient with severe left ventricular outflow tract obstruction has a stroke volume that depends on maintaining adequate preload and afterload. Important hemodynamic goals include avoiding tachycardia and increases in myocardial contractility, and regimes that include large doses of propofol or volatile agents are contraindicated. Patients with dilated cardiomyopathy and decreased ventricular function similarly should not receive agents in doses that further depress myocardial contractility or significantly alter preload or afterload. Patients with significant pulmonary hypertension should have a regimen that avoids large increases in catecholamine secretion from noxious stimuli that could precipitate a pulmonary hypertensive crisis. Chapter 17 discusses hemodynamic management, and Chapters 21–28 present the pathophysiology and anesthetic considerations for each of the major congenital cardiac lesions in detail.

To date, there have been few, if any, controlled studies of anesthetic regimen and cardiovascular outcomes in CHD; no agent or regimen is proscribed for any particular cardiac lesion, and there are many different approaches for each lesion among experienced pediatric cardiovascular anesthesiologists. However, careful consideration of the cardiovascular effects of the drugs and the patient’s pathophysiology and desired hemodynamic goals should allow the pediatric cardiac anesthesiologist to devise a safe and effective anesthetic plan for patients with CHD.

**KEY POINTS: ANESTHETIC REGIMEN SELECTION**

- Review all data carefully and construct a set of desired hemodynamic goals for each patient considering their unique pathophysiology.
- Design an anesthetic drug strategy that is likely to achieve the optimal hemodynamic state.
- Carefully monitor and titrate anesthetic drugs and prepare to change strategies if hemodynamic goals are not achieved.

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A full reference list for this chapter is available at: [http://www.wiley.com/go/andropoulos/congenitalheart](http://www.wiley.com/go/andropoulos/congenitalheart)


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ing an approximately 5% decrease in MAC for every degree
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CHAPTER 7
Cardiopulmonary Bypass

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Introduction

On May 6, 1953 John H. Gibbon, Jr. successfully performed, for the first time, open-heart surgery using cardiopulmonary bypass (CPB) for the closure of a large atrial septal defect. The heart–lung machine, consisting of a simple oxygenator in conjunction with roller pumps, took over the function of the heart and lungs for a duration of 26 minutes. The machine worked properly during the total bypass time of 45 minutes, apart from some fibrin formation on the oxygenator due to inadequate anticoagulation [1]. Gibbon’s success stood at the end of approximately 20 years of developing a heart–lung machine. In a 1937 publication, Gibbon published his first results of an experimental CPB in cats. In 1939 the former president of the American Association of Thoracic Surgeons, Leo Eloesser, said during a discussion following a lecture by Gibbons that his presentation reminded him of the seemingly impossible, fantastic stories of the novel writer Jules Verne that later often became reality [2]. In a series of 19 consecutive bypass uses in dogs, 12 of the animals survived. But the idea of perfusion with artificially produced circulating arterial blood did not originate with Gibbon. The idea was first documented in 1812, inspired by the French physiologist César Julien-Jean Le Gallois. In his monograph “Expériences sur le principe de la vie” he described experiments to define the relationship of respiratory, nervous system, and blood circulation. On August 9, 1951, in Turin, Dogliotti and Constantini used a partial bypass on humans for the first time [3]. When a patient whose condition during the surgical removal of a large mediastinal tumor drastically deteriorated, a heart–lung machine was used to maintain perfusion for 20
minutes and the patient was stabilized. On March 16, 1943, Willem Johan Kolff observed, during the clinical use of an artificial dialyzer, that oxygen was quickly absorbed by a cellulose membrane. This observation was the basis for the development of membrane oxygenators. Later Kolff presented the design of the first membrane oxygenator at the first Congress of the American Society for Artificial Internal Organs on June 5, 1955 [4]. Also in the 1950s Arthur Keats, Denton Cooley, and colleagues at Texas Children’s Hospital pioneered several important breakthroughs in congenital cardiac surgery with bypass, including, in 1959, the first description of heparin–protamine titration [5]. In a seminal 1958 article, they described anesthetic problems in their first 200 cases of congenital heart surgery with bypass, which included bypass times; changes in blood gases, electrolytes, and lactate; cardiac rhythm disturbances; and blood transfusions [6]. The first commercial oxygenators became available in the 1960s and the number of open cardiac surgery procedures increased rapidly at that point. Subsequent attempts to use the heart–lung machine to help correct complex congenital heart defects in small infants were hindered by high morbidity and mortality rates until Barratt-Boyes and Castaneda started using deep hypothermic circulatory arrest in the late 1960s and early 1970s. Less than two decades later, pediatric cardiac surgery and anesthesia had progressed to providing multistage palliation for infants with single-ventricle physiology. Today CPB is a standard feature of daily pediatric cardiac anesthesia practice. Advances in neonatal CPB techniques over the past 60 years have been among the most important factors leading to improved outcomes in pediatric cardiac surgery. Extracorporeal perfusion in newborns, infants, and children is in many aspects different from the adult patient. This is caused by the underlying physiologic changes as well as the different pathophysiology secondary to shunt physiology.

In this chapter we review the equipment and techniques used in CPB, with a primary focus on neonatal and pediatric bypass. We will also summarize the effects of CPB on different organ systems. Extensive reviews on the multi-organ effects of congenital cardiac surgery are presented in Chapter 8, and neurological monitoring and outcomes in Chapter 11. In this chapter we emphasize specific management issues that occur in daily practice. Further details on specific technical issues can be found in excellent extensive textbooks on the topic [7].

**Basic bypass circuit setup**

A basic bypass circuit (Figure 7.1) consists of a venous reservoir, an oxygenator/heat exchanger unit, roller pumps for perfusion, suction, and cardioplegia and the connecting tubing, cannulae, as well as monitoring and alarm devices. There are major differences between adult and pediatric CPB, stemming from anatomic, metabolic, and physiologic differences in these two groups of patients (Table 7.1). Much progress has been made in the miniaturization of circuits and components. Current technology allows a total priming volume as low as 95 mL for a neonatal circuit setup allowing transfusion-free repairs in smaller patients down to the 5–10 kg range in some institutions [8–10].

**Cannulation and tubing**

The selection of cannulas occurs on the basis of flow requirements and the anatomic relations. Single-stage venous cannulation is rare and selective superior and inferior vena cava cannulation plus an additional cannulation of a left persistent superior vena cava are routine. Thus, the infant patient routinely has an aortic cannula and two venous cannulas. A second aortic cannula may be used for cases of interrupted aortic arch to perfuse the descending aorta (Figure 7.2). Particular care must be observed during inferior vena cava (IVC) cannulation, as obstruction or malposition into a hepatic vein can occur. Addition of a small cannula for venting the systemic ventricle places significant demand on the surgeon to manage the position of the multiple cannulae in the small pericardial space of neonates and young infants. Venting the heart through an existing patent foramen ovale or atrial septal defect, or creating a small atrial communication is the preferred method for many congenital cardiac surgeons, instead of a cannula in a superior pulmonary vein, to avoid damage to these delicate structures.

In daily clinical practice, the amount of systemic venous return on CPB is directly correlated with the amount of pump flow, and vice versa. Venous drainage is often limited by the small size of the cannula and tubing as well as individual characteristics, the circuit used, and the use of accessory systems. Generally, venous drainage is obtained by gravity, placing the venous reservoir of the CPB circuit about 30 cm lower than the level of the heart; in this way a negative pressure equivalent to about 20–25 mmHg is obtained. This is adequate for the vast majority of adult patients undergoing conventional procedures. In pediatric patients, however, where relatively small-size cannulas and tubing of the venous circuit are used to reduce the pump priming volume, vacuum-assisted venous return is most often used. In this system, a constant vacuum (up to 80 mmHg) is created in the airtight venous reservoir, allowing more blood to be drained from the patient via the venous line. This system allows the performance of surgical procedures on CPB, even in small infants, without the need for large-size venous tubing and, therefore, without increasing the volume of the pump priming [11,12]. The major potential limit in the clinical application of this system is the risk of generating gaseous microemboli in the venous circuit. If the arterial pump is stopped for various reasons and the vacuum source is left on the venous reservoir, microbubble transgression can occur from the gas compartment to the liquid compartment of the oxygenator, creating another source of gaseous microemboli as soon as the arterial pump is turned on again [9,13].
Arterial cannulation is usually via the ascending aorta. Exceptions, however, are frequent in the newborn with malformation of the ascending aorta (e.g., interrupted aortic arch and hypoplastic left heart syndrome [HLHS]). In that case scenario, the ductus arteriosus is primarily cannulated to maintain body perfusion on bypass and the pulmonary arteries are snared to prevent runoff until an anatomic correction takes place.

The clinician must also be aware that femoral cannulation is not feasible in small children < 15 kg because of the small vessel size. Thus, on repeat sternotomy, this method of establishing CPB is usually not an option and careful retrosternal dissection must take place.

The aortic cannula represents the smallest diameter in the pediatric CPB circuit. The bypass tubing is responsible for the large foreign surface area and priming volume. The strategic selection of tubing dimensions can reduce the volume effectively (Tables 7.2 and 7.3). For example, in a 3.5 kg newborn with an approximate blood volume of 300 mL, the addition of a cardiotomy suction line of 6.3 mm (1/4 in.) diameter and with a total length of 250 cm would require approximately one-third of the patient’s blood volume (82.5 mL) before reaching the reservoir.

Malposition of cannulas is particularly problematic in pediatric perfusion. Systemic perfusion may be adversely impacted when placement of either venous or arterial
Table 7.1 Differences between adult and pediatric cardiopulmonary bypass

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Adult</th>
<th>Pediatrics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature</td>
<td>Rarely below 32°C</td>
<td>Commonly 18–20°C</td>
</tr>
<tr>
<td>Deep hypothermic circulatory arrest (DHCA)</td>
<td>Rare</td>
<td>Common for arch repair (HLHS, IAA)</td>
</tr>
<tr>
<td>Pump prime</td>
<td>Crystalloids</td>
<td>Blood components and albumin</td>
</tr>
<tr>
<td>Dilution</td>
<td>25–33%</td>
<td>Up to 200%</td>
</tr>
<tr>
<td>Perfusion pressure</td>
<td>50–80 mmHg</td>
<td>30–50 mm Hg</td>
</tr>
<tr>
<td>Flow rates</td>
<td>2.5 L/min/m² or 50–65 mL/kg/min</td>
<td>0–250 mL/kg/min</td>
</tr>
<tr>
<td>pH management</td>
<td>Alpha-stat</td>
<td>pH-stat</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Rare, only in hepatic injury</td>
<td>Common due to low hepatic glycogen stores</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>Frequent, increases mortality</td>
<td>Less common, may be protective</td>
</tr>
<tr>
<td>Cannulation techniques</td>
<td>Standardized, mostly ascending aorta and single-stage venous cannula</td>
<td>Variable, including ductus, aorta, main pulmonary artery; mostly bicaval venous cannulation</td>
</tr>
<tr>
<td>Ultrafiltration</td>
<td>Rare</td>
<td>Standard modified ultrafiltration or conventional ultrafiltration</td>
</tr>
</tbody>
</table>

HLHS, hypoplastic left heart syndrome; IAA, interrupted aortic arch.

Figure 7.2 Aortobicaval cannulation in a neonate. SVC, superior vena cava; IVC, inferior vena cava.

Table 7.2 Cardiopulmonary bypass tubing volumes

<table>
<thead>
<tr>
<th>Tubing diameter (in.)</th>
<th>Volume per meter length (mL/m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/2</td>
<td>126</td>
</tr>
<tr>
<td>3/8</td>
<td>71</td>
</tr>
<tr>
<td>1/4</td>
<td>33</td>
</tr>
<tr>
<td>3/16</td>
<td>18</td>
</tr>
</tbody>
</table>

Table 7.3 Cardiopulmonary bypass tubing sizes

<table>
<thead>
<tr>
<th>Arterial and venous tubing sizes</th>
<th>Patient weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>3/16 in. arterial line, 1/4 in. venous line</td>
<td>&lt; 10 kg</td>
</tr>
<tr>
<td>1/4 in. arterial line, 3/8 in. venous line</td>
<td>&lt; 20 kg</td>
</tr>
<tr>
<td>3/8 in. arterial line, 3/8 in. venous line</td>
<td>&lt; 50 kg</td>
</tr>
</tbody>
</table>

cannulas is not ideal. If venous obstruction occurs, the consequences are magnified because of low perfusion pressures. If the IVC cannula causes venous obstruction in the splanchnic bed, increased hydrostatic pressure causes ascites, and reduced perfusion pressure results in significant renal, hepatic, and gastrointestinal dysfunction. Obstruction of the superior vena cava (SVC) may produce an increase in intracranial pressure and result in decreased cerebral perfusion pressure and cerebral edema. It is possible to observe preferential flow to one side of the cerebral circulation or down the distal aorta (Figure 7.3). Transcranial Doppler monitoring of cerebral flow velocity or cerebral oximetry can provide an early warning of altered flow patterns caused by cannula misplacement [11]. Cooling patterns demonstrating rectal cooling preceding nasopharyngeal cooling may suggest a disproportionate amount of pump flow being directed away from the cerebral circulation [13].

Pumps

The two pumps most commonly used for CPB are roller pumps and centrifugal pumps. Roller pumps have the advantages of simplicity, low cost, ease and reliability of flow calculation, and the ability to pump against high resistance without reducing flow. Disadvantages include the need to assess occlusiveness, spallation of the inner tubing surface, which potentially produces particulate arterial emboli, capability of pumping large volumes of air, and the ability to create large positive and negative pressures. Centrifugal pumps offer the advantage of lesser air pumping capabilities, less ability to create large positive and negative pressures, less blood trauma, and virtually no spallation. Disadvantages include higher cost, the lack of occlusiveness (creating the possibility of accidental patient exsanguination), and afterload-dependent flow requiring constant flow measurement. In the setting of
short-term CPB for cardiac surgery, it remains uncertain whether the selection of one pump over another is of clinical significance; most institutions employ roller pumps for congenital heart surgery.

**Oxygenator**

The efficiency of gas exchange in the natural lung is mainly attributable to the large surface area generated by the airway and circulatory networks and the low resistance to diffusion. These same features are essential to the design of an efficient artificial lung. Other necessary features of an ideal oxygenator include minimal trauma to blood, thromboresistance, minimal reaction with blood components, minimal generation of gaseous microemboli, the ability to maintain performance over long periods, low prime volume, consistent physical properties, reliability, ease of use, and low cost. The efficiency of a membrane oxygenator is two to three times less than the efficiency of the natural lung at rest, and about eight times less than the natural lung under conditions of maximal exercise. The primary limiting factor to efficient gas exchange in membrane oxygenators appears to be blood phase resistance to both $O_2$ and $CO_2$ diffusion. A second factor that has limited the use of microporous membranes in situations of long-term extracorporeal support is the progressive decrease in gas exchange function. The most common microporous membrane oxygenator design in clinical use is the hollow-fiber type in which the polypropylene membrane is formed into fibers that are bundled or woven together. The fibers are 200–250 $\mu$m in diameter and 10–15 cm long, and the membrane thickness is 25–50 $\mu$m. Although the existence of micropores in the membrane significantly increases the gas exchange of membrane oxygenators, long-term use results in the progressive wetting of the surface, plasma leakage through the pores, and subsequent deterioration of membrane performance, thus limiting its use to acute CPB procedures. The newest oxygenators incorporate an arterial line filter to reduce priming volumes.

**Priming**

Bypass prime composition and volume are adapted to the particular requirements of the patient. The composition, however, is often a matter of opinion and differences are as great as the number of pediatric heart centers. If there is a consensus, it is probably only with regard to reducing volumes to a minimum to reduce transfusion requirements and dilutional effects of the patient [8,14].

Despite recent advances in technology, the majority of neonates and infants still require perioperative transfusion of homologous blood components. The lower the body weight of the patient, the more banked blood products need to be added to the prime. To maintain colloid osmotic pressure and a minimal amount of coagulation factors, albumin and fresh frozen plasma (FFP) are added. The most suitable priming in neonates seems to be the combination of albumin or FFP and red blood cells in such proportions so as to maintain the hematocrit (Hct) at about 28–30% during normothermia. A few centers are still able to obtain fresh whole blood (<48 hours after donation) for neonates, but outcomes of studies using this technique vs. “reconstituted” whole blood (FFP plus packed red blood cells [PRBCs] from the same or different donors) are conflicting [10,15,16]. Albumin is reported to maintain colloid osmotic pressure (COP; normally around 20–25 mmHg) and reduces fluid accumulation [8,10,17,18], while adding FFP to the prime maintains COP, increases the level of coagulation factors and reduces intraoperative transfusion requirements in complex neonatal and cyanotic cases [12,19]. However, postoperative transfusion requirements are not affected despite higher fibrinogen concentrations and better thrombelastographic values at the end of CPB [9,20]. The level of ionized calcium is adjusted, as all blood products contain significant amounts of citrate. This can lead to acute hypocalcemia and cardiac arrest with initiation of bypass. In addition, added erythrocyte concentrates should be as fresh as possible (<3–5 days old) to avoid hyperkalemia and hyperlactemia as side-effects. The reasons for this suggestion are that the level of 2,3-diphosphoglycerate in stored red blood cells decreases, metabolic load increases (potassium and lactate levels by the end of the second day are up to 7–25 mmol/L [11,21]), and the risk of complications with bypass is higher. The risk is particularly high in infants <5 kg if the prime contains irradiated blood [13,22]. If the red blood cells in the prime are older than 5 days, a prime blood gas
Table 7.4  Estimated patient blood volumes by weight

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Estimated blood volume (mL/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3 (neonate)</td>
<td>90</td>
</tr>
<tr>
<td>3–10</td>
<td>85</td>
</tr>
<tr>
<td>10–20</td>
<td>80</td>
</tr>
<tr>
<td>20–30</td>
<td>75</td>
</tr>
<tr>
<td>30–50</td>
<td>70</td>
</tr>
<tr>
<td>&gt;50</td>
<td>65</td>
</tr>
</tbody>
</table>

should be checked and corrected. Circulating and filtrating the prime for 20 minutes alleviates most of these problems. Alternatively, processing packed red blood cells via a cell saver is reasonable and may add additional benefits such as the avoidance of hyperglycemia, high citrate levels, and hyperkalemia [14–16,23,24]. In addition, lactate levels are reduced and microaggregates > 20 μm are eliminated. Care must be taken to avoid using normal saline as a washing solution, as a hyperchloremic metabolic acidosis can be induced in newborns and infants. In addition, the use of cell-saving devices during pediatric cardiac surgery provides another means of reducing banked blood exposure [25]. A desirable practice is to adjust the prime composition in neonates and small infants to the patient’s blood, with pH, Na⁺, K⁺, Ca²⁺ and temperature within narrow ranges.

Packed red blood cell requirements can be calculated on the basis of weight and starting Hct. The change in Hct, ΔHct, is calculated as follows:

$$\Delta \text{Hct} = \frac{\text{Hct}_{\text{PAT}} \times \text{BV}_{\text{PAT}}}{\text{BV}_{\text{PAT}} + \text{PV}}$$

where HctP is patient hematocrit, BV P is the patient blood volume (see Table 7.4) and PV is the priming volume. The transfusion requirement is calculated as:

$$\text{PRBC (ml)} = \text{Hct}_{\text{PAT}} \times \left( \frac{\text{BV}_{\text{PAT}} + \text{PV}}{\text{BV}_{\text{PAT}} \times \text{Hct}_{\text{PAT}} - \frac{60\%}{}} \right)$$

where 60% is the average Hct of stored PRBCs. After initial prime composition, an Hct on the prime can be measured, and a further adjustment before CPB is made to achieve Hct in the goal range. In newborns, a goal Hct on pump of 30–35% is maintained. Older patients or special circumstances (e.g., severe hypoxia) may require adjustments to a lower limit of around 25% or higher than 30% (severe hypoxia), even though both limits are controversial. Historically, many centers permitted marked hemodilution on CPB to avoid transfusion. Recent studies question this approach and provide evidence of improved neurological function when higher Hcts are maintained during CPB. A randomized controlled clinical study in infants undergoing CPB demonstrated adverse perioperative and developmental outcomes with extreme hemodilution [26]. This issue remains controversial, although the clinical data in support of higher Hcts of at least 25% are compelling [27,28]. Also hemostasis may be improved by higher Hct levels.

**KEY POINTS: BASIC BYPASS CIRCUIT SETUP**

- The basic bypass circuit consists of the venous reservoir, the oxygenator/heat exchanger unit, roller pumps for perfusion, suction, and cardioplegia and the connecting tubing, cannulae, as well as monitoring and alarm devices.
- The oxygenator contains an integrated arterial filter.
- Priming for children < 10 kg includes either fresh whole blood or reconstituted blood prime with PRBCs and/or FFP.
- Target hematocrits on bypass are > 25% with a goal of > 35% for neonates and complex cyanotic lesions or > 28% for acyanotic lesions.

**Differences between pediatric and adult CPB circuitry**

Major differences need to be considered when dealing with the pediatric patient on CPB (Table 7.1). These include the degree of hemodilution, flow rates and perfusion pressure, temperature, cannulation, prime and blood gas management, ultrafiltration, hemodynamic management, and, in certain cases, the presence of aortopulmonary collaterals.

**Hemodilution**

Recent efforts to minimize circuit volumes have led to the development of smaller circuit elements. However, there continues to be a gross degree of hemodilution realized in the neonatal patient. This can be as much as three to 15 times the amount of hemodilution seen in an adult. For example, in a 3 kg child given 85 mL/kg, an estimated blood volume (EBV) of 255 mL contrasts with an average circuit prime volume of 300–400 mL. Thus, a prime:EBV ratio can exceed >2–3:1, or >100–150% of a neonate’s blood volume.

In the average adult circuit, only a 25–33% dilution rate is realized. This degree of dilution necessitates the addition of donor blood up to a body weight of approximately 10 kg to maintain an adequate Hct for optimal oxygen delivery on bypass.

**Perfusion pressures**

Management of the pediatric patient undergoing CPB is made difficult by competing hemodynamic goals for the brain, heart, and viscera. The brain is protected from
hypoperfusion by systemic vasoconstriction and pressure autoregulation. However, extreme hypotension can exceed the dilatory reserve of cerebral resistance vessels and place the brain at risk. In the future, continuous monitoring of pressure autoregulation may be performed using near-infrared spectroscopy (NIRS) as a surrogate of CBF by using the cerebral oximetry index (COx). The COx is a moving correlation between arterial blood pressure and cerebral oximetry and is able to evaluate individual autoregulatory thresholds [29].

Perfusion pressures in the neonate can be quite low, less than 30 mmHg. This is often due to the lack of reactivity of the neonatal vasculature or presence of a shunt like a patent ductus arteriosus (PDA). With meticulous management of blood gases, Hct, temperature, and flow rates, the goal should be the minimal use of vasoconstricting agents (i.e., phenylephrine) to maintain an ideal blood pressure. As a rule of thumb, perfusion pressure (MAP [mean arterial pressure] – CVP [central venous pressure]) goals in the neonate are 30–40 mmHg, and over the first 2 years of life the target perfusion pressures increase to 40–50 mmHg. At best, normal flow rates are combined with reasonable perfusion pressures to reach all tissue beds, including those that require a certain opening pressure for function (kidney, brain, splanchnic bed). One should also keep in mind that the lower limit of myocardial perfusion pressure is around 15 mmHg, calculated as MAP – CVP. This is relevant for diastolic pressures below 30 mmHg.

Flow rates

The flow rates for neonates are quite variable, ranging from 0 to 200 mL/kg/min. Deep hypothermic circulatory arrest (DHCA) is at one end of the spectrum, contrasted with high metabolic demands, vent return, circuit shunts, or patient collaterals, all of which contribute to the necessity of high flow rates at the other end. This can often exceed a cardiac index of 3 L/min/m². The flow rates are calculated on the basis of weight, but the perfusionist must adapt flows according to the individual case and to demands. One strategy is to employ standard full flow rates in neonates and infants up to 10 kg of 150 mL/kg/min. With hypothermia and decreased metabolic demands, many centers will reduce flows to 80–100 mL/kg/min to reduce venous return to the field, lowering flows further to 25–50 mL/kg/min during deep hypothermia for intracardiac complex repairs.

Blood gas management

It is the current practice in some institutions to employ pH-stat management on all cases in which temperatures are taken to hypothermic levels. In this temperature-corrected strategy, the PCO₂ remains unchanged from 37°C (40 mmHg). This strategy allows for cerebral vasodilation and more even cooling. The corrected PCO₂ ranges at 37°C can be >80–100 mmHg.

Aortopulmonary collaterals

Uncommon in adults, but fairly common in patients with chronic cyanosis with decreased pulmonary blood flow, aortopulmonary collaterals can be a challenge. Flow rates are frequently affected and temperatures may need to be lowered substantially to accommodate lower bypass flows to reduce blood return to the operative field. Flows may need to be decreased in conjunction with the use of vasodilating agents. Phenolamine 0.1 mg/kg and nitroglycerine are the drugs of choice during cooling and rewarming, titrated to effect. Phenylephrine is contraindicated and would only enhance collateral flow.

Temperature ranges

As a very basic comparison, there is a trend toward conducting adult cases at tepid or normothermic temperatures while many neonatal cases are still utilizing cold temperatures with or without DHCA. However, more and more neonatal cases are performed at mild hypothermia. The perfusion considerations are multiple and this topic is discussed in a separate section on hypothermia and DHCA.

Glucose management

It is of the utmost importance to maintain euglycemia in the neonate. Although there are increased glycogen stores in the neonatal myocardium, there are low hepatic glycogen stores. Exogenous glucose may be necessary in the early neonatal period to maintain normal glucose levels and should be continued into the pre-bypass period.

Perfusion considerations on CPB are directed at efforts to maintain normal glucose levels such as washing packed cells or minimizing glucose content in cardioplegia or intravenous (IV) fluids. When glucose levels are greater than 300 mg/dL, a saline hemodilutional washout with the hemocconcentrator is utilized. Frequent monitoring is recommended. Levels should be maintained at approximately 150 mg/dL just prior to DHCA.

Hyperglycemia worsens neurological injury, as elevated glucose levels result in increased anaerobic metabolism of glucose and increased lactic acidosis. This leads to further depletion of ATP. Hypoglycemia alone can be treated, but coupled with hypothermia, cerebral blood flow may be compromised by altering autoregulation. This can be further exacerbated with hyperventilation, as this may occur in weaning a patient with pulmonary hypertension from CPB. Overall, tight glycemic control (blood glucose level in the range 80–110 mg/dL) is not indicated in children as the outcome was not any different from standard care in the intensive care unit (ICU) [30]. Hyperglycemia was not associated with lower neurodevelopmental outcomes at 8 years of age in the Boston Circulatory Arrest Study. However, lower glucose measurements below 90–100 mg/dL after CPB were associated with a higher risk of EEG seizures. The authors speculate that limiting glucose as an important energy substrate for the neonatal brain, which
may have increased requirements under conditions of low CPB flows or DHCA, may be a reason for this association [31]. In a more contemporary study of 93 neonates undergoing the arterial switch operation, patients with more than 50% of the intraoperative and early postoperative periods spent at glucose values between 80 and 110 mg/dL had more perioperative complications than those with > 200 mg/dL more than 50% of the time [32]. The practice of many pediatric cardiac anesthesiologists is to maintain plasma glucose levels in the 100–200 mg/dL range for neonates and small infants.

**Equipment**
One circuit size for the adult patients at a given institution can adequately provide flows for patients from 50 kg and more. Most pediatric centers employ two or three circuits on the basis of the patient’s weight, procedure, and flow requirements.

**Ultrafiltration**
Utilization of ultrafiltration in some form, whether it be conventional or modified, is seen in > 90% of our neonatal and pediatric cases. Several system modifications may be necessary to allow for these options.

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**KEY POINTS: DIFFERENCES BETWEEN PEDIATRIC AND ADULT CPB**

- The major differences between pediatric and adult CPB are the degree of hemodilution, flow rates, and perfusion pressures.
- Hemodilution is exaggerated and can reach more than 150% of the patient’s blood volume.
- Flow rates are in the range of up to 200 mL/kg/min or an equivalent cardiac index of 3.0 L/min/m² and higher can be found in the neonate.
- Aortopulmonary collaterals can be a challenge during bypass and should be managed with vasodilators and increased flow rates.
- pH-stat is the preferred method of blood gas management during cooling in pediatric cases using deep hypothermic circulatory arrest.
- Glucose management with targets of 100–200 mg/dL is desirable.

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**Management of pediatric CPB**

**Stages of CPB**
Cardiac cases using CPB can be divided into several basic phases: pre-bypass period and anticoagulation, bypass period with initial cooling, cross-clamping and myocardial protection, reperfusion of the heart, separation from CPB, modified ultrafiltration and hemostasis, and, lastly, sternal closure and transfer to the ICU.

**Pre-bypass period**
The pre-bypass period begins with surgical incision and lasts through to initial dissection and preparation for cannulation. During this period, transesophageal echocardiography (TEE) is performed to confirm the diagnosis and establish a basis for post-bypass comparison. Baseline activated clotting time values are obtained and metabolic abnormalities are corrected. Cannulation of the great vessels just prior to CPB can often precipitate arrhythmias, hypotension, and arterial desaturation, especially in small infants and children. Ventilation may need to be limited to minimize lung excursion to allow precise cannulation in small infants. Coordination with the surgeon is particularly important. Hemodynamic stability is maintained by cautious fluid administration and small boluses of vasopressors, as necessary. After placement of the aortic cannula, pressure in the aortic root is measured by the perfusionist through the cannula in situ and should be close to the MAP of the patient.

A small volume infusion of 2–5 mL/kg is often used at that point to ensure unobstructed aortic cannula flow before bypass. If the aortic cannula is already in place, it is common practice to coordinate the administration of volume between the anesthesiologist and perfusionist while the surgeon completes cannulation.

**Anticoagulation and hemostatic management**
Development of the coagulation system is incomplete at birth and continues in the postnatal period until the age of about 6 months. This increases the risk of bleeding disproportionately in the neonatal and infant group up to 1 year or approximately 8 kg of weight [33–35]. Coagulation in cyanotic infants may be particularly impaired secondary to polycythemia, lower fibrinogen levels, low platelet count and abnormal platelet function [36], decreased concentrations of factors V, VII, and VIII, and increased fibrinolysis [37,38].

Of particular importance is the role of antithrombin III (ATIII) levels that do not reach adult values until 3–6 months. This low level of ATIII may reduce the ability of heparin to provide anticoagulation adequate to prevent thrombin generation during CPB in infants [33,37,39–41] and an exaggerated inflammatory response may occur [33,37,38,42,43]. Infants may require an initial heparin dose of 400 units/kg or higher. It has also recently been shown that in infants with CHD, levels of other thrombin inhibitors are depressed compared with healthy infants. This may partially explain the high levels of thrombin generation during infant CPB. The coagulopathy induced by CPB affects children more profoundly than adults. There are many factors implicated, including hemodilution, contact activation, and initiation of a systemic inflammatory response. Despite large doses of heparin during CPB, heparin does not block thrombin generation completely but partially inhibits thrombin after it is produced. Thrombin is continuously generated and
A consumptive coagulopathy is initiated [39,41]. The lower potential of newborn plasma to generate thrombin might in part downregulate thrombin markers during CPB. This, however, does not seem significant enough to completely prevent the subsequent reperfusion-induced thrombin peak [37,38,42–44]. Thromboelastography has actually shown that neonates and infants develop faster and stronger clots than adults [33–35,45]. In addition, acquired coagulation defects in 58% of non-cyanotic and 71% of cyanotic infants have been reported [36,46–48]. If thrombin formation could be completely inhibited during CPB, the consumption of coagulation proteins and platelets could largely be prevented. Initial heparin doses range from 300–400 units/kg bolus before cannulation, to 200–400 units/kg in the circuit, and 50–100 units/kg ongoing administration every 30–120 minutes. Heparin’s peak therapeutic effect occurs within 2 minutes. CPB may delay the peak effect by 10–20 minutes from hypothermia or hemodilution. Plasma binds 95% of heparin with some uptake by the extracellular fluid, alveolar macrophages, splenic/hepatic endothelial cells, and vascular smooth muscle. The plasma half-life is dose-dependent (i.e., 126 ± 24 minutes at a dose of 400 units/kg vs. 93 ± 6 minutes at a dose of 200 units/kg) [33–35,49]. Heparin is metabolized by the reticuloendothelial system and eliminated by the kidneys. Hypothermia and renal impairment, but not hepatic impairment, delay elimination. A roughly linear relationship exists between heparin dose and the activated clotting time (ACT) if certain criteria are maintained [36,50], namely normal ATIII and factor XII activities, normothermia, near-normal platelet function, a platelet count > 50,000/dL, and fibrinogen concentration > 100 mg/dL. However, in children the correlation is rather poor [37,38,51]. An ACT is measured before heparinization and repeated a minimum of 3 minutes after giving heparin. CPB is not initiated until an adequate ACT or heparin level is confirmed.

Given the variability in the ACT, heparin concentration can also be measured directly. A two-point (straight line) dose–response curve assists in judging how much additional heparin to administer. Acceptable levels during CPB are 2–4 units/mL, and in the newborn population up to 6 units/mL. This regimen increases required heparin doses on CPB, but results in lower protamine doses and less blood loss [40,52]. The optimum method of assessing adequate anticoagulation during CPB in children has thus not yet been defined and much work is still required in this area. The use of heparin-coated biocompatible perfusion circuits is probably helpful in reducing the degree of activation of the coagulation system in children [42,43,53,54], but it is rather expensive and has not gained wide acceptance.

The optimal ACT for CPB is controversial. Although the minimum recommended ACT is 400 seconds, others recommend 480 seconds [39,41,55], as heparin only partially inhibits thrombin formation. This is done to minimize the consumptive coagulopathy that may result from barely adequate anticoagulation. Failure to achieve a satisfactory ACT may be due to inadequate heparin or to low concentrations of ATIII, or “heparin resistance.” [44,56]. Increases in acute-phase reactant proteins such as factor VIII and fibrinogen commonly shorten the APTT and may appear as heparin resistance.

If 500 units/kg of heparin fail to achieve an adequate ACT, ATIII deficiency becomes more likely and FFP or recombinant ATIII (30 IU/kg) [45,49] is necessary to increase antithrombin concentration.

### Initiation of CPB and flow requirements

After heparinization and cannulation, CPB is initiated by opening the venous outflow cannula to the reservoir. Slow decompression of the heart and maintaining a minimal output of the beating heart reduce the drop in blood pressure due to the hemodilution. Based on weight or body surface area, a flow requirement is calculated. The cardiac index is approximately 25–50% greater than that of an adult. For newborns, a flow of 2.6–3.2 L/min/m² is recommended and for infants a flow of 2.4–2.6 L/min/m² is sufficient. If normothermic CPB is chosen, flow rates in the range of 3.0–3.5 L/min/m² are required [46–48,57]. This can be reduced during hypothermia (Figure 7.4) [58]. Infants have a much more compliant vasculature, which results in lower perfusion pressures on CPB. Causes of severe hypotension after initiation of bypass can be the presence of hemodynamically relevant shunts (e.g., major aortopulmonary collateral arteries) previously placed systemic to pulmonary artery (PA) shunt or a PDA, which both lead to a circulatory steal in the systemic circulation, requiring higher flows and possibly early control by the surgeon. Increased bronchial and non-coronary collateral flow draining into the left atrium can be a particular problem, especially in cyanotic children, with a resultant significant negative impact on myocardial protection during periods of aortic cross-clamping. Because of the small and easily obstructed

![Figure 7.4 Nomogram relating oxygen consumption to perfusion flow rate and temperature. X indicates clinical flow rates used by Kirklin and Barrett-Boyes [58]. (Source: Kirklin & Barrett-Boyes [58]. Reproduced with permission of Elsevier.)](image-url)
vena cavae in infants, careful assessment for venous obstruction is carried out immediately after initiation of bypass. The patient’s head and face are assessed for signs of venous obstruction including plethora and cyanosis of the scalp and face, distended fontanelle, and decrease in cerebral oxygen saturation to levels below baseline. If a central venous catheter has been placed with its tip in the SVC, pressures should be low (i.e. <5 mmHg) and at times are negative if placement is adjacent to the SVC cannula. Venous return judged by the volume in the venous reservoir is continually monitored by the perfusionist, with a sudden decrease prompting communication with the surgeon to investigate the cause.

The adequacy of perfusion is monitored by the usual parameters. These are MAP, the in-line measurement of mixed venous saturation, pH, base excess, and the regular testing of blood for heparin levels and lactate and other indices of end-organ perfusion (e.g., urine output, somatic and cerebral oxygenation values [NIRS, for example]).

### Cooling and temperature management

Systemic cooling is utilized for nearly every case. Hypothermia is classified as mild (30–36°C), moderate (22–30°C), or deep (17–22°C). In general, lower temperatures are used for more complex operations that carry a greater potential for requiring periods of low-flow bypass or circulatory arrest. Cooling is primarily achieved through the heat exchanger in the bypass circuit, although surface cooling with lower ambient air temperatures or forced air warming systems set to lower temperatures is used in some institutions. Infants have a high ratio of surface area to body weight. Infants also have an immature thermal autoregulatory center. Because of these factors, wide fluctuations in body temperature occur easily. Warming and cooling on bypass occur much more readily. If the clinician is not careful, cooling can occur too rapidly, and deep brain structures may become dangerously cold. There is evidence to suggest that cooling too rapidly is deleterious to neurological function. Thus, it is important to cool slowly, evenly, and completely, and most investigators recommend at least 20 minutes of cooling if circulatory arrest is used (i.e., no faster than 1°C/min) [59]. The opposite is also true. It is very easy to warm too rapidly and for hyperthermic overshoot to occur. Recent data suggest that hyperthermia can be very damaging, and temperature differences of even 1°C or 2°C are highly significant [60]. Monitoring should include nasopharyngeal, rectal, and arterial inflow temperatures. Rewarming the patient should occur at less than 8°C temperature difference between heat exchanger and patient blood temperature, with maximal inflow temperatures of 37.0°C to avoid the formation of micro air bubbles [61–63]. Special bypass techniques such as regional cerebral perfusion (see later) have been developed to avoid the necessity of using DHCA, and may also be performed during this time.

### Aortic cross-clamping, myocardial ischemia, and protection

Repair of most congenital heart lesions is becoming more feasible. Perioperative myocardial damage remains the most common cause of morbidity and mortality after successful surgical repair. Thus, effective myocardial protection assumes an even greater role than in the adult, as perioperative insults are less well tolerated and more difficult to treat. Neonatal hearts may be difficult to protect because of immaturity, cyanosis, hypertrophy of the right ventricle, complex coronary artery pattern, and duration of ischemia to achieve a good repair.

The neonatal heart is ultrastructurally immature. Myofibrils are arranged in a disorderly fashion and have a smaller percentage of contractile proteins than do those in the adult (30% vs. 60%) [64]. The immature heart shows fewer mature mitochondria and a lower oxidative capacity [65]. Control of myocardial contractility in infants depends more on adrenal function and circulating catecholamines than on direct autonomic influences. There are also differences in myocardial calcium metabolism. In the mature myocardium, the sarcoplasmic reticulum is the predominant source of calcium ion for excitation–contraction coupling, but the sarcoplasmic reticulum is poorly developed in the immature heart (see Chapter 5). Because the neonatal myocardial cell is deficient in T-tubules, it is incapable of internal release and reuptake of calcium for contraction and instead depends heavily on transmembrane calcium transport for myocardial contraction. These differences in calcium handling by the cell provide some explanation for the clinical observation that newborns require greater serum ionized calcium levels for optimal myocardial contractility. Experimental evidence suggests that the newborn myocardium tolerates ischemia and reperfusion better than the adult heart. However, in practice, pediatric patients undergoing cardiac surgery have a greater incidence of low cardiac output postoperatively than adults. The discrepancy between the experimental evidence and the clinical experience may relate to the cardiac anomalies involved. Ventricular hypertrophy and cyanosis are common, and the hypertrophied heart has been found to have decreased subendocardial blood flow [66] and lower concentrations of high-energy phosphates before arrest. Chronic cyanosis has been associated with a decreased threshold for anaerobic metabolism during stress [67], diminished myocardial reserve [68], asynchronous left ventricular wall motion [69], and downregulation of β-adrenergic receptors [70]. Reoxygenation injury with release of oxygen free radicals upon initiation of CPB can further exacerbate the pre-existing injury [71]. The abrupt increase in oxygen levels on bypass in chronically hypoxic infants leads to the loss of antioxidant reserve capacity and subsequent loss of myocardial function. Preventive measures include leukodepletion of blood prime, use of in-line arterial filters and normoxic management (PaO₂ of 80–100 mmHg) initiating bypass. Over the course of 10–20 minutes, FiO₂ can be increased to obtain PaO₂ levels in the
For example, bypass prime composition is adjusted to myocardial protection is taken by many institutions. The cornerstone of myocardial protection in pediatric cardiac surgery is hypothermia. Systemic hypothermia is, to some degree, used in nearly all congenital cardiac repairs. It is particularly important in cyanotic infants with increased non-coronary collateral flow to the heart. Myocardial protection can be problematic in these cases because of cardioplegia washout and rewarming of the myocardium. Because systemic hypothermia allows reduced flow rates, it decreases myocardial collateral flow. Blood cardioplegia is often used in adults, but its advantages may be lost in infants undergoing deep hypothermia. However, if greater cardioplegic temperatures are used (warm cardioplegia), there is a clear advantage to the use of blood cardioplegia [72]. The optimal electrolyte composition of cardioplegia for pediatric patients is controversial. There is great institutional variation among solutions used. A certain amount of calcium is necessary in the solution to prevent the severe injury that may result from calcium paradox [73]. However, excessive amounts are deleterious. The addition of magnesium, a natural calcium antagonist, may solve this dilemma. Increasing the ionized magnesium level has been shown to improve postoperative rhythm stability and reduce calcium-induced mitochondrial dysfunction during reperfusion. Thus, in the absence of magnesium enrichment, hypocalcemic cardioplegia results in adequate myocardial protection in stressed hypoxic hearts. Magnesium was particularly beneficial during normocalcemic cardioplegia solution [74]. In addition to the specifics of cardioplegia administration reviewed in the following, a multifaceted approach to myocardial protection is taken by many institutions. For example, bypass prime composition is adjusted to closely match the patient’s blood with regard to pH, serum Na⁺, K⁺, Ca²⁺, and temperature. Initiation of bypass in a neonatal heart with cold, acidic, hypocalcemic, hyperkalemic prime is a significant stress-increasing risk of inadequate myocardial protection. Gentle surgical handling of the heart by the primary surgeon and assistants is also felt to play a role, with excessive traction felt to disrupt the delicate fibrous skeleton of the heart, rendering less efficient the coupling of the myofibrils to mechanical force transduction of the heart. Gentle handling of the myocardium also lessens the risk of arrhythmia such as ventricular fibrillation, which on bypass represents an ischemic state of the heart. Monitoring carefully for the return of any cardiac electrical activity is important, giving consideration to more frequent cardioplegia dosing. Aggressively treating ventricular tachycardia, and especially fibrillation, on bypass is very important. Meticulously maintaining venous drainage with proper cannula size selection and positioning, as well as venting of the left side of the heart prevents ventricular distension and subendocardial ischemia. Maintaining cold myocardial temperatures with ice slush application is also utilized to preserve a low-energy consumption state. There is some evidence that volatile anesthetics can provide a degree of myocardial preconditioning when administered before CPB, in the setting of adults undergoing coronary bypass surgery. The cellular mechanisms are complex but are demonstrated to include mitochondrial and sarcoplasmic potassium-ATP channel opening, transcription factors (NF-KB, HIF-1 alpha), new proteins (iNOS, COX-2), and mediators (NO, PGE, neutrophil inhibition). There is limited pediatric data, and no clinical studies have been published, so it is not clear if this strategy is effective for neonatal and infant myocardial protection [75].

**Induction and maintenance of cardioplegic cardiac arrest**

Two basic methods of cardioplegic arrest are used: blood cardioplegia or crystalloid cardioplegia. The superiority of either method is still controversial [76]. Histidine-tryptophan-ketoglutarate (HTK), an intracellular crystalloid solution, has been widely used clinically for cardioplegic arrest during cardiac surgery. The HTK solution can offer sufficient cardiac protection to the neonatal heart for up to 2 hours of ischemia and it provides equivalent myocardial protection to multidose cold blood cardioplegia with reduced transfusion requirements [77]. However, clinically significant hyponatremia can occur and severe fluctuations in sodium concentration should be corrected [78]. During induction, some institutions use warm blood cardioplegia with amino acid supplementation in stressed, hypoxic hearts to recover the intracellular energy stores before arrest [79]. This results in complete preservation of myocardial function, particularly in the chronic, hypoxic heart that might become ischemic under situations of stress.

After aortic cross-clamping and sequestration of the coronary circulation, cardioplegia is generally administered in an antegrade fashion into the aortic root. As the neonatal heart lacks stenotic lesions, adequate distribution is not an issue. Perfusion pressures should be in the normal range of diastolic blood pressures and should not be higher than 30–50 mmHg. Higher pressures can lead to myocardial edema, particularly in the neonatal hypoxic heart [80]. The need for multidose cardioplegia in infants is controversial [81]. There is some evidence that multidose cardioplegia may actually lead to poorer structural and functional recovery [82]. It was postulated that this worsened injury may be an effect of increased permeability of the immature microvasculature, resulting in myocardial edema.

Myocardial collaterals are more important in neonatal hearts and can quickly lead to rewarming of the myocardium. Profound hypothermia or the reduction of flow can only provide limited additional protection,
as other vital organs can be compromised (brain, kidney). Periodic reapplication of blood cardioplegia at intervals of 10–20 minutes counteracts non-coronary collateral washout.

Retrograde cardioplegia is utilized by some surgeons in selected situations, including cases that include an open aortic root and coronary artery translocations or transfers [83]. These include Ross procedures, arterial switch operations, and aortic root replacements. Retrograde cardioplegia is also used in some cases of severe aortic insufficiency where the ability to arrest the heart with standard aortic root cardioplegia is impaired. A small cannula, i.e. 6 Fr., is placed under direct vision into the coronary sinus, and cardioplegia is infused at pressures not exceeding about 50 mmHg. Because pediatric patients rarely have coronary stenosis, retrograde cardioplegia is used infrequently, and many surgeons prefer to avoid it altogether. Instead, the aortic root is opened immediately after cross-clamping, and cardioplegia solution is infused directly into each individual coronary artery ostia with special cannulae.

**Reperfusion**

Reperfusion is considered the phase when the coronaries are reperfused with regular systemic blood flow after cross-clamp removal and the patient is fully warmed. A few minutes before cross-clamp removal, lidocaine and magnesium sulfate may be administered to reduce the incidence of ventricular arrhythmias often seen after unclamping. Before aortic cross-clamp removal, TEE can be used to assist the surgeon in de-airing maneuvers, which may include manipulation of the heart and “milking” any intraventricular air through the aortic valve and out of the cardioplegia cannulation site. The patient may be positioned in Trendelenburg position before cross-clamp removal to avoid air bubbles being ejected into the cerebral circulation. This period is an important time in the course of cardioplegic arrest, as many mechanisms of cellular damage are completed during reperfusion. Optimally, normal sinus rhythm and myocardial contractility are restored during this time, while the patient is slowly rewarmed. In adults, reperfusion with warm blood before unclamping the aorta improved metabolic and functional recovery. Substrate-enriched reperfusion with the amino acids aspartate and glutamate, however, results in full recovery of function in infants [84]. Depending on the total ischemic time of the heart (aortic cross-clamp time), the heart requires time to restore the ATP stores in the myocardium. In general, 10–15 minutes are considered the minimum time requirement. For longer cross-clamp times, 25% of the time is considered appropriate as reperfusion time at our institution. The release of the cross-clamp often leads to a drop in blood pressure due to the higher release of anaerobic metabolites from the heart which cause vasodilation to a greater degree compared with the adult. This hypotension should not be treated by administration of calcium at this point to reduce the risk of immediate reperfusion injury. In addition, at this time air can be ejected into the right coronary artery, resulting in acute ischemia with ST-segment elevation and poor myocardial contractility; this is best treated with higher perfusion pressures and adequate time on CPB to allow passage of air through the coronary system and recovery of the myocardium. Calcium chloride 10–20 mg/kg can be administered to the CPB circuit or to the patient immediately before separating from bypass to correct the slight hypocalemic state of CPB and improve myocardial contractility, but should be avoided during the first 15 minutes of reperfusion of the heart. Additional doses of calcium are added to maintain normal levels of ionized calcium after bypass in neonates and infants, particularly as calcium and other electrolytes are lost quickly through the use of modified ultrafiltration and the infusion of citrate-rich blood products.

**Separation from CPB and post-bypass phase**

During rewarming, surgery is completed, and inotropic and vasoactive agents are started, but only after the ECG and myocardial contractility have improved to near normal. The rationale is that increasing myocardial oxygen demand too early in the post-ischemic heart may be detrimental. Ventilation commences after manual ventilation lung recruitment maneuvers, administration of nebulized β-agonist agents, if indicated, and thorough suctioning. The lungs are inspected visually if the pleura have been opened for complete inflation and deflation and any areas of atelectasis are addressed with inspiratory holding breaths near the patient’s vital capacity. Severe ventilation problems may rarely need to be assessed with fiberoptic bronchoscopy for accurate assessment of endotracheal tube placement, and further suctioning of secretions. Hemofiltration and blood transfusion are used to achieve the desired Hct. Pressure transducers are re-zeroed and leveled. Left atrial and/or PA monitoring lines, if indicated, are placed at this time, as are temporary atrial and/or ventricular pacing wires. Forced air warming devices, circulating water mattress, and ambient temperature are adjusted to desired levels. If the patient is incompletely rewarmed before separation from CPB, a significant temperature drop with precipitous post-bypass reduction in core body temperature can occur (“after-drop”). This may lead to vasoconstriction, shivering, increased oxygen consumption, and acidosis. However, post-ischemic hyperthermia can lead to delayed neuronal cell death and predispose to arrhythmias such as junctional ectopic tachycardia [85]. Mild degrees of hypothermia and certainly the avoidance of hyperthermia are essential in the perioperative period [86]. In the pediatric patient group, rectal temperature mostly reflects peripheral temperature. Several endpoints have been proposed, such as nasopharyngeal temperatures greater than 35.0°C, bladder temperature greater than 36.2°C [87] or skin temperatures greater than 30°C [88]. We use an...
endpoint of 35.5°C rectal temperature, which is supported by the literature [89]. Cardiac rhythm is carefully assessed, and if the desired sinus rhythm at an adequate rate has not been achieved, atrial and/or ventricular pacing are instituted. If arrhythmias occur that have the potential to compromise hemodynamic status after CPB, they are treated before separation with pharmacologic approaches or internal cardioversion.

Finally, blood gas values are measured before weaning from CPB to optimize electrolytes and Hct. Once the patient is ventilated, warm and in a stable rhythm, in addition to all the post-CPB requirements being met, weaning is initiated by slowly decreasing the venous return. Arterial perfusion is continued until the appropriate filling is reached. If all parameters are stable, modified ultrafiltration is started. The heart is observed carefully during this process to avoid overfilling or to recognize right heart failure early on. Also, radial artery pressure may not be accurate following CPB and tends to underestimate both the systolic and mean central aortic pressures. A questionable pressure should be confirmed with central aortic pressure measured from the aortic cannula. A pulse oximeter waveform appearing immediately after termination of CPB is a sign of good peripheral perfusion and adequate rewarming. There may be a larger arterial–alveolar gradient between end-tidal carbon dioxide and arterial carbon dioxide tension at the end of bypass due to ventilation–perfusion mismatch. A rapidly increasing area under the curve of the capnograph and increasing end-tidal CO₂ are signs of good cardiac output and pulmonary status during the termination of CPB.

### Conventional ultrafiltration and modified ultrafiltration

The application of the CPB machine in children leads to a significant capillary leak more often than is the case in adults. This is caused by the relatively larger foreign surface area exposure and the resulting greater inflammatory response.

Hemofiltration has been defined as ultrafiltration with the return of intravascular replacement fluids to compensate for losses. In contrast, ultrafiltration simply removes fluid from through a convective process involving filtration across membranes. Conventional ultrafiltration (CUF) during CPB or modified ultrafiltration (MUF) after the end of bypass both reduce levels of proinflammatory cytokines and total interstitial body water after extracorporeal circulation. CUF or MUF are therefore standard procedures in all pediatric perfusion systems. The most commonly used procedure is MUF, first described by Naik et al. [90,91]. In this case, the bypass circuit is modified and the flow reversed at the end of CPB before protamine is given. Blood from the aortic cannula is directed through a hemofilter (blood flow rate of 100–300 mL/min) and infused back into the right atrium after warming and oxygenation. The ultrafilter pump is run at 10–30 mL/kg/min ultrafiltrate removal, with a vacuum on the ultrafilter. Replacement intravascular volume is infused from the venous reservoir as necessary. Several different methods of deciding when to terminate MUF are employed; some surgeons simply use a cutoff time of 15–20 minutes and others stop when the circuit volume has become diluted or when the desired Hct has been reached. Frequently, the surgeon’s patience is the limiting factor. Filtering also will be stopped if the patient becomes hemodynamically unstable. Multiple beneficial effects can be observed (see Table 7.5); particularly important are the increase in Hct, the reduction of cytokines, improved myocardial perfusion, and a reduction in pulmonary vascular resistance (PVR) with improvement of right heart function. A steal phenomenon has been described whereby excessive flow rates divert blood from the aorta to the hemofilter, leading to cerebral and systemic deoxygenation. Disadvantages of MUF are a delay in heparin reversal and decannulation of approximately 10–20 minutes, as well as the possibility of hemodynamic instability, if preload is not adequately maintained by the perfusionist. However, surgical hemostasis can be carried out during this time period. The combination of MUF after CPB with zero balance conventional ultrafiltration on bypass can eliminate additional unnecessary volume from cardioplegia or irrigation. The use of filtration during CPB (as conventional, dilutional, or zero balance ultrafiltration) also removes inflammatory mediators and vasoactive substances [92,93]. Studies [94] have shown that compared

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Effect</th>
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<tbody>
<tr>
<td>PVR, PAP</td>
<td>Decreases due to oxygenation and warming</td>
</tr>
<tr>
<td>Stroke volume, CO</td>
<td>Left ventricular stroke volume increases secondary to improved pulmonary blood flow</td>
</tr>
<tr>
<td>SVR, blood pressure</td>
<td>Increases due to the reduction of vasoactive substances (interleukins, bradykinin, etc.)</td>
</tr>
<tr>
<td>Hemoglobin, hematocrit</td>
<td>Increases due to hemoconcentration</td>
</tr>
<tr>
<td>Interstitial body and lung water</td>
<td>Decreases secondary to water removal</td>
</tr>
<tr>
<td>Improved gas exchange [65]</td>
<td>Improved V/Q mismatch</td>
</tr>
</tbody>
</table>

PVR, pulmonary vascular resistance; PAP, pulmonary artery pressure; SV, single ventricle; CO, cardiac output; SVR, systemic vascular resistance; V/Q, ventilation–perfusion.

Source: Elliott et al. [94]. Reproduced with permission of Elsevier.
with control patients, patients who have modified ultrafiltration after bypass have substantially less increase in total body water, have less interleukin-8 (IL-8) and complement in their bloodstream [95,96], require less blood transfusion [97,98], show improved coagulation factors [99,100] and faster recovery of systolic blood pressure [90], pulmonary function [101], and cerebral metabolic activity [102]. Modified ultrafiltration performed after CPB reverses hemodilution and decreases tissue edema and thereby accelerates postoperative recovery [103]. The combined use of ultrafiltration of prime solution, zero-balance ultrafiltration on bypass and MUF strategy seems to be the most effective method, even though the principal clinical outcomes are similar between modalities [104].

Failure to separate from CPB
Occasionally, despite escalating inotropic support, a child is unable to maintain adequate cardiac output and systemic oxygen delivery and therefore a return to CPB must be considered. An assessment of arterial blood gas and Ca$^{2+}$ values, and whether intended inotropes are infusing correctly is important. Immediate TEE evaluation should be performed for the possibility of residual defects that require surgical attention. If no further surgical intervention is warranted, the source of the difficulty in weaning from CPB should be sought and other therapies must be considered. Is the Hct level adequate for this child? Too much hemodilution can lead to decreased systemic vascular resistance (SVR). The ideal Hct depends on the pathology and is probably in the range of 35–45% for complex repairs. Is the SVR too low? In children with low SVR who are either non-responsive to catecholamine infusions or who are experiencing adverse effects due to catecholamine therapy, arginine vasopressin has been shown to be a potent vasoconstrictor, with infusions resulting in increased MAPs and decreased catecholamine dependence. Its use in children appears promising when cardiac function is adequate [105,106]. Fixed doses of 0.01–0.04 units/kg/hour of vasopressin are used. Exposure to endotoxin and cytokines as on CPB can trigger a de novo synthesis of the inducible, calcium-dependent isoform of nitric oxide synthase. Methylene blue inhibits this process by decreasing intracellular cyclic guanosine monophosphate concentrations through guanylate cyclase inhibition, thus blocking its vasodilator properties. It increases arterial pressure, SVR, and left ventricular stroke work, but does not increase cardiac output, oxygen delivery, or oxygen consumption. Methylene blue in a dose of 2 mg/kg followed by 1 mg/kg/hour has been used successfully in the setting of perioperative vasoplegia in adults [107], neonatal sepsis [108], and in a case report of infective endocarditis in a 10-year-old girl [109]. Side-effects are rare in doses < 2 mg/kg, but pulmonary hypertension and other side-effects can occur with repeat doses [110]. Is the right heart failing? Pulmonary hypertension with resultant right heart failure may occur post-CPB, either as a result of long-standing increases in PA pressures or PVR, now exacerbated by the effects of CPB, or as a result of acute increases in PA pressures or PVR secondary to protamine administration. Management has been challenging, as IV medications often affect both SVR and PVR. Selective pulmonary vasodilation became possible with the introduction of inhaled nitric oxide (iNO), an endothelium-derived vasodilator that is rapidly deactivated by hemoglobin [111]. Several groups of patients have been shown to potentially benefit from iNO administration post-CPB [112,113]. Patients with single-ventricle physiology undergoing total cavopulmonary anastomosis (Fontan procedure) with elevated PVR post-CPB, as well as children with elevated pulmonary venous pressures secondary to total anomalous pulmonary venous connection or congenital mitral stenosis, frequently show improvement with administration of iNO. For patients on iNO, caution should be exercised when transporting from the operating room to the ICU in order to avoid interruption of therapy, as rebound pulmonary hypertension and rapid clinical deterioration may occur. Other options to lower PVR include sildenafil 0.5 mg/kg through a nasogastric tube [114], IV sildenafil, or nebulized prostacyclin [115]. In the event that severe left or right ventricular dysfunction persists in the absence of residual anatomic defects that can be surgically corrected, consideration may be given to continued mechanical support of the circulation. Currently, immediate pediatric options for mechanical circulatory support are extracorporeal membrane oxygenation or short-term left ventricular assist device in neonates, infants, and children. These techniques are most useful when recovery of ventricular function is expected within 24–72 hours, or when cardiopulmonary support is unavoidable. See Chapter 32 for further details.

Heparin reversal and transfusion management
During modified ultrafiltration, cardiac function and the quality of the surgical repair are assessed via TEE, and if found to be satisfactory, protamine is administered to neutralize residual heparin after completing MUF. In small infants and palliated anatomies, the goal Hct separating from bypass should be 40–45%. This improves hemodynamic stability and allows immediate correction of coagulation disorders by infusion of blood products.

Protamine 1–1.5 mg/kg is given for each 100 units of the initial heparin dose to reverse its effect. This assumes that any further doses are given to maintain a heparin level and prevents overdosing of protamine with its associated effects on platelet function (reduction of the interaction of the glycoprotein Ib receptor with von Willebrand factor) [116]. If the ACT is still elevated or CPB prime (heparinized) blood is reinfused into the patient, an additional 25% of the initial dose of protamine is added and the ACT rechecked. However, particularly in infants, the administration of protamine and the persistent treatment of a suspected incomplete heparin reversal should not distract and delay the treatment of other
commonly associated post-bypass coagulopathies such as thrombocytopenia, platelet dysfunction, and other coagulation factor deficiencies [117–120]. An individualized management of anticoagulation and its reversal results in less activation of the coagulation cascade, less fibrinolysis, and reduced blood loss and need for transfusions [52], while improving the clot stability as assessed by thrombelastography. However, care should be taken not to overdose the total amount of protamine [121,122]. After one-third to one-half of the planned protamine dose is administered, blood from the surgical field must not be returned to the cardiotomy reservoir to avoid circuit thrombosis in case it is necessary to reinitiate bypass. An ACT or heparin level confirms adequate heparin neutralization. More protamine (0.5–1 mg/kg) can be given if either test remains prolonged and bleeding is a problem. Hypotensive protamine reactions can occur when protamine complexes with heparin because complement is released. This is much less common in children than in adults. Hypotension can be attenuated by adding calcium chloride (2 mg/mg protamine). Pediatric protamine reactions are rare, occurring in 1.7–2.8% of patients undergoing CPB [123]. Life-threatening reactions to protamine represent true allergic or pulmonary hypertensive reactions. Protamine reactions should be treated with epinephrine as the first-line agent and careful volume resuscitation as required. For severe reactions, it may be necessary to readminister heparin and resume CPB. Hemostatic management can be guided by thrombelastography. Newer devices allow a full “point-of-care” functional assessment of the coagulation within 10–15 minutes [124]. A recent retrospective study of 100 infants assessed before and after a heparin–protamine titration system (Hepcon®, Medtronic Corp. Minneapolis, MN, USA) reported that more limited protamine dosing neutralized heparin but also prevented anticoagulation effects (prolonged R values on thromboelastography [TEG]) caused by excessive protamine [121]. Further details can be found in Chapter 13.

Antifibrinolytic therapy

Bleeding is more common in pediatric cardiac surgery patients than in adults. Both qualitative and quantitative abnormalities in coagulation proteins have significant functional sequelae, which influence the hemostatic responses to CPB. Cyanotic CHD itself is associated with coagulation abnormalities, including platelet abnormalities and fibrinolysis. There is extensive published research on the use of aprotinin and lysine analog antifibrinolytics to modify the adverse effects of CPB in adults, but for pediatrics, their dose and effects are much less clear.

Two agents are currently available to modify the hemostatic response to CPB: ε-aminocaproic acid (EACA) and tranexamic acid (TA). Aprotinin, an established esterase inhibitor, has been withdrawn from the market due to safety concerns in adult patients and will only be discussed briefly.

EACA and TA

Both EACA and TA appear effective in reducing bleeding and transfusion in cyanotic patients, provided an adequate dose is administered. Their efficacy in other high-risk and mixed populations is not as well established. Contrary to aprotinin, they seem to lack significant clinical anti-inflammatory efficiency beyond their effects on coagulation [125,126]. Suppression of excessive plasmin activity may play an important role in the generation of proinflammatory cytokines during and after CPB [127]. For an excellent and detailed recent review, please refer to Eaton [128].

Aprotinin

Aprotinin is a non-specific serine protease inhibitor derived from bovine lung. Aprotinin is believed to exert its effects through inhibition of kallikrein and plasmin, with decreased hemostatic activation, inhibition of fibrinolysis, and preservation of platelet function. Kallikrein is part of the contact activation that accelerates the activation of the hemostatic, inflammatory, and fibrinolytic systems during CPB. Aprotinin appears to decrease bleeding and transfusion requirements in specific circumstances. The study by Mössinger et al. [129] illustrates the potential of aprotinin on less blood loss in pediatric heart surgery. Sixty patients weighing < 10 kg undergoing primary corrective congenital heart surgery with CPB were enrolled and were less likely to be transfused with red blood cells and cryoprecipitate. Aprotinin dosing was based on published pharmacokinetic data [130]. A more recent meta-analysis of aprotinin in pediatric cardiac surgery found a 33% reduction in the proportion of children receiving blood transfusions [131].

In addition, aprotinin suppressed thrombin activation, inhibited D-dimer production, and improved postoperative PO2/FiO2 ratios [129]. The duration of mechanical ventilation in treated patients was less than half that of controls. Interestingly, the authors failed to show a difference in multiple biochemical measures of the inflammatory response, including IL-6, IL-8, and IL-10. Complement C3 was lower in treated patients only at 4 and 24 hours postoperatively. These findings were not seen in a small trial on neonates where aprotinin had no effect on outcome variables [132]. Concerns about the safety of aprotinin have been raised in the recent past mostly related to one of three areas: thrombosis, renal effects, and anaphylaxis [133–143]. However, results from a large multicenter database do not reflect the risk profile seen in the adult population [144].

Dosing

Aprotinin dosing

Aprotinin dosing studies suggest that a continuous infusion is necessary to maintain effective plasma levels on CPB; an initial loading dose should be at least 30,000 KIU/kg, and the pump prime dose should be based on the volume of the bypass prime, rather than the weight of the patient.
TA dosing
Chauhan et al. [145], in a dose-ranging study of TA published in 2004, found the most effective dosing scheme of the four studied to be a 10 mg/kg load, 10 mg/kg in the pump prime, and 10 mg/kg after protamine. More recent pharmacokinetic studies have shown effective concentrations of 20 μg/mL [146] using a dosing schedule with 6.4 mg/kg followed by 2–3.1 mg/kg, depending on weight [147]. Continuous and discontinuous doses of TA effectively inhibit fibrinolysis [148]. A high-dose regimen leading to blood concentrations greater than that required for D-dimer inhibition may be more efficient than lower dosages [149].

EACA dosing
Based on a pharmacokinetic study [150], the initial loading dose is 75 mg/kg, a pump priming dose of 75 mg/kg followed by an infusion of 75 mg/kg/hour to establish and maintain a therapeutic plasma concentration (130 μg/mL) in 95% of patients.

Rapid IV injection of TA or EACA may cause hypotension. We infuse loading doses over approximately 20 minutes.

Comparison studies of antifibrinolytics
With the considerable variability among studies of the three drugs under consideration in terms of design, dose, and outcomes, it is difficult to draw any conclusions about relative efficacy from the literature. There are a few published comparison studies. Chauhan et al. [151] compared low-dose aprotinin, EACA, and the combination in 300 cyanotic patients undergoing cardiac surgery. There was no difference between EACA-treated and aprotinin-treated patients in any measured variable. The same group compared TA and EACA in a placebo-controlled study of 150 patients with cyanotic CHD [145]. Both drugs were superior to placebo, but there were no significant differences between the treated groups with respect to 24-hour blood loss, transfusion or re-exploration rate. Finally, the effects of aprotinin and TA were compared in 100 children, evenly divided into four groups: placebo, TA, aprotinin, and a combination of the two drugs [152]. Again, all treatment groups fared better than placebo in 24-hour blood loss and transfusion, with no significant differences among the three treated groups. Thus, the limited comparative evidence would suggest that the three drugs are equivalent in efficacy for reduction of bleeding and transfusion, at least with the doses and patients studied, and there is little or no advantage to combination therapy.

In summary, evidence supports the efficacy of the lysine analog antifibrinolytics EACA and TA, and aprotinin to decrease bleeding and transfusion in pediatric patients undergoing cardiac surgery involving CPB. This benefit is likely to be more significant in high-risk groups, such as cyanotic patients, newborns, complex surgeries, and reoperations. Aprotinin seems to have the strongest anti-inflammatory capacity of the antifibrinolytics [153].

The safety profile of these drugs is not fully understood, but each may have significant side-effects that require further research in the future [154–156].

**KEY POINTS: MANAGEMENT OF PEDIATRIC CPB**

- Pre-bypass, 300–400 units/kg heparin are injected to reach a target ACT > 400 seconds.
- Two methods of cardioplegic arrest are used: hyperkalemic blood cardioplegia or hyponatremic crystalloid cardioplegia.
- Reperfusion after unclamping should be at least 8–10 minutes or 25% of the total cross-clamp time.
- Separation from bypass is initiated after resumption of ventilation and reduction of venous outflow to fill the heart.
- Conventional ultrafiltration during CPB and modified ultrafiltration after CPB are commonly employed.
- Afterwards, heparin reversal is achieved with protamine, and coagulation disturbances are corrected with platelets and other coagulation products, guided by ACT and/or laboratory diagnostics (e.g. TEG).
- The antifibrinolytics aprotinin, TA and EACA are effective and used in most surgeries with increased risk of bleeding.

**Effects of CPB on organ systems**

Cardiopulmonary bypass-induced systemic inflammatory response syndrome (SIRS) is a host response to the exposure of blood components to the foreign surface of the CPB circuit and initiation of the complement cascade. The early inflammation phase is triggered as soon as blood comes into contact with the synthetic circuit by activation of F-XII (coagulation factor) and C3 (immune factor) [157–159], and the late phase, following release of the aortic cross-clamping, is driven by ischemia–reperfusion and endotoxemia. As a consequence, pro- and anti-inflammatory mediators are released into the circulation and the balance between these two groups of mediators is probably more important than the absolute levels of any of them [158–164]. Hypothermia and transfusion, frequently associated with pediatric CPB, are also two non-specific factors activating the inflammatory response [158–160,162,164–167]. Hypothermia modifies the metabolism of inflammation biomarkers by delaying, rather than decreasing, inflammatory systemic response [157–160,162,164,166,167]. Furthermore, genetic factors are involved in the inflammatory response and may account for inter-patient variability [158–169]. Although the lungs are often the primary organ targeted, SIRS after CPB may be severe enough to affect other end-organ
function. One of the major challenges is how to modulate the systemic inflammatory response, not only to control the drawbacks of inflammation but also to preserve a level of inflammation needed for host defense and wound healing. This should be the goal of further research.

Currently, there are a number of strategies being employed targeting prevention of SIRS and multisystem organ failure, including the use of corticosteroids, protease inhibitors, thromboxane inhibitors or antagonist, prosta-cyclins, complement inhibitors, and cytokine inhibitors, including monoclonal antibodies and IL-1 receptor antagonist. With the exception of corticosteroids, all of these other approaches are experimental and thus far have not shown a beneficial effect on clinical outcomes, even though some have shown the intended effect on their molecular targets.

Multiple studies in children on corticosteroids have consistently shown a reduction in inflammatory response, with some demonstrating improvement in clinical outcome [159–170]. A limiting factor in some studies using corticosteroids has been the lack of effect on clinical outcome and the higher incidence of postoperative infections and renal dysfunction with increasing cumulative corticosteroid exposure [161,152,165,171–174]. The routine prophylactic use of steroids therefore cannot be recommended and may only be indicated in high-risk patients (DHCA, arterial switch operation) [171,172].

There is also evidence that pulsatile flow significantly decreases endotoxin levels. An explanation could be the improved microcirculation and end-organ perfusion during pulsatile perfusion [173,174]. However, there is a paucity of clinical studies demonstrating an outcome difference with this technique, and so it has not been widely adopted in pediatric perfusion practice. For further details on the mechanism of end-organ dysfunction and treatment, refer to Chapter 8.

**Neurological injury and protection**

Brain injury in children with CHD has been documented before and after surgery for CHD. Some complications are apparent soon after the operation, such as seizures, stroke, and coma, whereas others appear long after the operation, such as cognitive deficits and psychomotor delay. Radiological and pathological studies have described a spectrum of brain lesions after pediatric cardiac surgery, located mainly in the neocortex, periventricular white matter, and basal ganglia, corresponding to the neurological deficits seen clinically [175,176]. These subtle defects manifest as a developmental signature that includes cognitive and intellectual impairment, attention and executive function deficits, visual–spatial and visual–motor skill deficiencies, speech and language delays, and behavioral difficulties. The spectrum of lesions is consistent with hypoxic–ischemic injury, contrary to mostly embolic events in the adult population. When this injury occurs – before, during, or after the operation – remains uncertain. Adverse neurological outcomes after neonatal cardiac surgery are multifactorial and related to both fixed and modifiable mechanisms. Fixed factors include known genetic syndromes, structural central nervous system malformations (an incidence of up to 29% in HLHS) [177], multiple surgeries (leading to multiple insults), blood flow patterns in utero, preoperative cerebral hypoxia, embolic events occurring during the balloon atrial septo-stomy procedure [177], socioeconomic status, and a poorly defined genetic predisposition. Potentially modifiable factors include preoperative hypoxia–ischemia, intraoperative use of DHCA, neutrophil activation of the brain [178–180], and postoperative cardiopulmonary derangements [181]. Some interventions that may limit brain injury from DHCA include preoperative steroids and aprotinin, hyperoxygenation before DHCA, allowing at least 20 minutes of cooling to ensure adequate cerebral protection, packing the head in ice, intermittent cerebral perfusion between 15- and 20-minute periods of DHCA (Figure 7.5), and modified ultrafiltration after CPB. Other modifiable factors of CPB management include optimal flow at all temperatures [182,183], the avoidance of extreme hemodilution [27] and emboli [184], pH-stat management [185,186], and modulation of the inflammatory response by the use of ultrafiltration and steroids [187]. According to a recent meta-analysis, the only intervention supported by a high degree of evidence is the avoidance of extreme hemodilution to Hct below 25% [187]. Whereas myocardial protection and systemic oxygen delivery are continuously monitored during neonatal CPB, adequate cerebral perfusion has traditionally been evaluated by surrogate markers such as perfusion pressure, mixed venous oxygen saturation, or base deficit and lactate levels. However, there are now real-time intraoperative cerebral monitoring devices available for clinical use, the potential benefits of which are becoming recognized [188]. The most widely used technologies include NIRS, transcranial Doppler, raw and processed electroencephalography, and serum measurement of S100B protein. Real-time technologies allow immediate interventions upon interruption of optimal cerebral flow and may improve outcome [189]. Improved strategies to prevent injury in these arenas are much needed [190]. For an extensive discussion of neurological monitoring and outcomes, see Chapter 11.

**Pulmonary effects**

Post-bypass lung injury may be a result of ischemia–reperfusion injury or may be associated with the systemic inflammatory response caused by extracorporeal circulation [191]. Alveolar injury is also associated with cyclic closing and opening of alveoli, with shear injury to the alveolar–capillary interface causing increased permeability and pulmonary edema with a significant pulmonary inflammatory reaction [192]. Etiologies of postoperative pulmonary dysfunction after CPB include a decrease in total lung capacity, functional residual capacity, atelectasis, pulmonary edema, increased inspiratory oxygen, and ventilation–perfusion mismatch [193].
Administration of 100% oxygen during CPB may lead to absorption atelectasis and oxygen toxicity. Lung injury could be prevented in a piglet model using continuous pulmonary perfusion on CPB [194]. In a study by Pizov et al. [195], lung function improved later postoperatively in patients ventilated with 100% oxygen during CPB. Several studies have assessed modes of ventilation on bypass and their effects. Continued ventilation throughout CPB is associated with superior postoperative respiratory function in certain clinical scenarios, possibly due to attenuation of the ischemia–reperfusion injury, but this technique has yet to gain wider acceptance. Maintaining ventilation and PA perfusion during CPB has shown some benefits in limiting pulmonary platelet and neutrophil sequestration, and attenuating thromboxane B₂ response after CPB [196,197]. To date, the evidence favoring continuous ventilation alone during CPB on cardiopulmonary function is inconsistent, with most studies showing no benefit [198–200]. At our institution, we prefer continued ventilation at low tidal volumes, room air, and low positive end-expiratory pressure (PEEP) settings in patients undergoing simple procedures without cross-clamping like a right ventricle–conduit exchange, etc. (if tolerated by the surgeon). Many surgeons will require total lung collapse to allow complete access to the heart, without movement, for neonatal and infant patients with limited intrapericardial space. In more complex cases, we start ventilation after thorough pulmonary toilet and suctioning with a recruitment maneuver. This is usually done in the context of de-airing and aortic clamp removal. Afterward, we continue ventilation at low settings with approximately 2 mL/kg and a PEEP setting of 5–8 cmH₂O with an FiO₂ of 0.21. Full ventilation is resumed just before weaning from bypass, usually in a pressure-regulated, volume-controlled mode to maintain minute ventilation with stable tidal volumes. The pressure limit is carefully monitored and set 5 cmH₂O above the upper inspiratory pressure.

Renal, hepatic, and gastrointestinal effects

Little is known about the epidemiology and risk factors for the development of acute renal failure in children post-CPB for cardiac surgery. The incidence of acute renal dysfunction complicating open-heart surgery in children is significant, at 11–17% [201,202]. Low cardiac output was a significant predictor of developing a renal injury. Other risk factors include young age, the preoperative need for mechanical ventilation, use of milrinone, gentamicin and furosemide, the duration of CPB and anesthesia and multiple cross-clamp times as well as the transfusion of blood products [203]. This is often related to the complexity of the operation. Unexpectedly, DHCA was not a predictor of postoperative renal dysfunction. On the one hand, better and more sophisticated surgical and CPB techniques are available, while on the other, children with more complicated cardiac lesions requiring longer CPB time are operated on today. There is also evidence that the neonatal kidney is more vulnerable to conditions of hemodynamic stress [202], with loss of autoregulation leading to blood pressure-dependent renal blood flow and ischemia-induced renal injury. All of these conditions render the neonate more prone to complications of ischemia than the older infant or child. Renal replacement therapy is required in 1.6–7.7% of patients. In children, the mortality rate in those requiring dialysis following...
CPB is reported to range from 46% to 67%. However, renal failure is often temporary. Among those who recover, 93–100% of survivors of renal replacement therapy after CPB surgery have normal renal function at discharge from hospital [204,205]. Peritoneal dialysis is a safe and effective treatment for children after CPB surgery and should be initiated early in the course of acute renal injury [206–210]. Peritoneal dialysis is also utilized in some centers routinely after complex neonatal and infant surgery, to counteract the frequent low urine production from antidiuretic hormone release and acute renal ischemic effects [208]. Peritoneal dialysis also effectively filters inflammatory mediators, and the overall result is to limit fluid accumulation and shorten the time of mechanical ventilation [211].

Plasma and urine neutrophil gelatinase-associated lipocalin thresholds are early predictive biomarkers for AKI [212]. Several investigations provide evidence that intestinal organ function is altered during CPB. Splanchnic, but not systemic, oxygen extraction increases during normothermic, non-pulsatile CPB. Splanchnic blood flow is not significantly affected by normothermic or hypothermic CPB at normal pump flows compared with the pre-bypass condition [213,214]. The increase in splanchnic oxygen extraction during hypothermia, indicating a splanchnic oxygen supply/demand mismatch, was therefore most likely caused by a decrease in splanchnic oxygen delivery, in turn caused by a decrease in hemoglobin concentration secondary to hemodilution. The splanchnic region might be more susceptible to a decrease in oxygen delivery by hemodilution, compared with other organs. Normothermic CPB leads to a loss of gastrointestinal (GI) barrier function independent of the duration of CPB. Current data indicate that intestinal mucosal autoregulation is maintained during CPB within the pressure range 50–75 mmHg [215]. Improving pump flow rather than infusing vasoconstrictive drugs to increase aortic pressure can improve both splanchnic and renal perfusion [216], and improve the postoperative course in children [217]. Although GI complications may have a low incidence (0.3–3%), they are associated with a high mortality (13–63%) [218,219]. Several risk factors (e.g., use of vasopressors, pre-existing comorbidities, perioperative hypotensive episodes, and valve surgery) have been evaluated for the development of alterations in GI organ function. Liver dysfunction rarely occurs after CPB.

**Endocrine and metabolic response to CPB**

In children, hypoalbuminemia and hyperchloremia are the predominant acid–base abnormalities after CPB, whereas lactic acidosis and wide ion gap acidosis are rare [220]. Hyperchloremia following CPB appears to be a benign phenomenon. By contrast, hypoalbuminemia, an alkalinizing force, was associated with a prolonged requirement for intensive care.

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**Figure 7.6 Relationship between cerebral oxygen consumption and nasopharyngeal temperature during bypass at a flow of 2 L/min/m².**
(Source: Kirklin & Barrett-Boyce [58]. Reproduced with permission of Elsevier.)
hypothermia on the myocardium. Reactivity of the microcirculation is impaired after deep hypothermia, as are many cellular functions. The lungs are very sensitive to CPB, and hypothermia may increase the capillary leakage more than normothermia by inducing microcirculatory dysfunction and impairing endothelial responses [224]. By reducing oxygen demand, hypothermia is effective in protecting the brain, but it impairs vasomotor and cerebral oxygen regulation [225], alters energy metabolism [226], and increases intracranial pressure, and overshoot during rewarming may induce neurological injury [227]. Furthermore, the protective effect of hypothermia on the inflammatory reaction and neurological recovery may have been previously overestimated [228]. The inflammatory reaction induced by CPB seems to be delayed rather than diminished by hypothermia [229]. Finally, with prolonged DHCA, long-term follow-up has shown impaired neurodevelopmental outcome [230]. Therefore, normothermic CPB, already commonly used in adult cardiac surgery, has been promoted and progressively extended into pediatric practice [231]. Favorable surgical results have been achieved with normothermic bypass for even complex operations such as the arterial switch operation [232].

Temperature is not the only characteristic of normothermic CPB. Other factors to be considered are flow and Hct. The flow generally used for mild hypothermic CPB is 2.0–2.4 L/min/m² (Figure 7.3). In normothermic CPB, pump flow is maintained throughout the procedure at 3.0–3.5 L/min/m². In terms of hemodilution on CPB, Hct is maintained above 30% during the procedure, with 40% by the end of CPB for normothermic CPB. Thus, normothermic CPB is better characterized by “normothermic, high-flow, high-hematocrit CPB” [57].

**Deep hypothermic circulatory arrest**

Hypothermia has been utilized since the early days of CPB to allow reduced flows in order to improve intracardiac surgical exposure. Bigelow et al. were the first to demonstrate in 1950 that hypothermia decreases the metabolic rate [233] (Figure 7.6). It decreases blood loss [231], provides myocardial protection [234], and, most importantly, is neuroprotective [235]. This mostly relates to the decrease in the metabolic rate by 64%, by cooling from 37°C to 27°C. Also, at a given temperature, the amount of gas in solution increases proportionally to the decrease in temperature (ideal gas law). In CPB, this translates to cooling the patient not only to lower the metabolic rate but also to obtain a higher solubility of oxygen in blood and tissues. Pearl et al. [236] were able to show that the use of hyperoxia with a pH strategy led to the lowest production of acids during 60 minutes of DHCA. This is probably related to increased tissue oxygen loading pre-arrest.

The disadvantages of hypothermia include disruption of cerebral autoregulation (Figure 7.7), prolongation of CPB, and a greater tendency toward postoperative bleeding [237]. Postoperative recovery, however, is not prolonged by hypothermia [238]. Also, the wound infection rate does not seem to be influenced by hypothermic bypass [239]. Hypothermia during cardiac surgery only gained widespread use after the development of a heat exchanger that could be integrated into the CPB machine [240].

Deep hypothermic circulatory arrest involves cooling the patient's body temperature to 17–18°C, stopping the bypass machine, draining the blood from the patient into the venous reservoir, and removing the cannulas from the heart. After the first reports of DHCA in the 1960s, this technique gained popularity in the 1970s and 1980s, because of the perfectly bloodless field it provided. This facilitated complex intracardiac and aortic repairs in newborns and small infants [241], as well as reducing edema. However, it soon became evident that DHCA was associated with neurological morbidity. Choreoathetosis, seizures, coma, and hemiparesis were all noted, especially with prolonged DHCA (>60 minutes) [242]. Clinical and experimental evidence suggests that DHCA preferentially damages the basal ganglia, which control tone and movement. The main input of the basal ganglia is the striatum, a highly dopaminergic region of the brain. Increases in free dopamine levels as an indicator of brain damage and cell disruption occur earlier in prolonged DHCA than in low-flow bypass strategies [243], and about 15 minutes earlier using alpha-stat versus pH-stat management [244]. It is interesting to note that the incidence of these acute morbidities seemed to increase when alpha-stat management became the accepted standard in many centers. Long-term adverse neurodevelopmental outcomes have also been associated with long periods of DHCA, including abnormalities in mental development [185], and in fine and gross motor skills. The Boston Circulatory Arrest Study is a remarkable achievement in which 180 newborns undergoing the arterial switch...
operation from 1988 to 1992 were studied, with follow-up now complete to the age of 16 years [245,246]. The CPB protocol in those years included alpha-stat management, routine hemodilution to a Hct of 20%, and the absence of an arterial filter on the CPB circuit. A DHCA time of greater than 41 minutes was associated with a significant increase in long-term neurodevelopmental problems. The effect of longer DHCA times was diminished, although still present at age 16 years with an association with lower visual-spatial scores and executive functioning. In the same patient cohort at age 16 years, shorter cooling time and higher nadir temperature were associated with impaired microstructural development of deep subcortical white matter when assessed with quantitative magnetic resonance imaging (MRI) [247]. In a recent study from a cohort of neonates undergoing surgery from 2004 to 2008, longer duration of DHCA was also associated with higher incidence of white matter injury on postoperative MRI [248].

Although the 41-minute cutoff is now a well-accepted limit in congenital heart surgery, multiple changes have subsequently been made to bypass protocols. Results from animal experiments utilizing a neonatal piglet model of DHCA, as well as data from the Boston Circulatory Arrest Study, led to the following recommendations for increasing the patient’s safety margin when utilizing DHCA:

- Hematocrit of 25–30% should be the target [249].
- Systemic hypothermia should be achieved slowly, over no less than 20 minutes (Figure 7.8).
- pH-stat blood gas management should be used, at least for cooling, to improve tissue oxygen loading and more even cerebral cooling (Figure 7.9) [250,251]. Core body temperatures of 17–18°C should be utilized, and ice bags should be applied to the head [252]. Hyperoxia immediately before DHCA improves tissue oxygen loading [237].
- DHCA should be divided into periods of no longer than 20–30 minutes, allowing a reperfusion period of at least 2 minutes between each segment of DHCA, to improve neurological outcome [253].
- Low-flow CPB (at greater than 40–50 mL/kg/min) offers greater cerebral protection than DHCA [254]; regional cerebral perfusion may be better than low-flow CPB (see later).
- Cold normoxemic reperfusion of the brain after DHCA for 5–10 minutes may be beneficial to restore cerebral autoregulation and wash out accumulated metabolites before adding the metabolic burden of rewarming to the brain [255]. Controlled reoxygenation was also associated with reduced myocardial damage, oxidative stress, and cerebral and hepatic injury in cyanotic children despite similar inflammatory responses to hyperoxia [256].
- Normoxemia should be maintained to decrease exacerbation of brain injury after DHCA [257]. Neurological monitoring is useful in the individual patient to aid in determining the safe duration of DHCA [250,258] (Figure 7.5).

Although there are situations where DHCA must be utilized, many surgeons are avoiding it whenever possible, minimizing its duration and dividing the periods of its use, or using alternative methods, such as regional cerebral perfusion.

Regional cerebral perfusion

In order to avoid the use of DHCA, several novel CPB techniques have been developed over the past 15–20 years to allow perfusion of only the brain during critical periods of surgery, such as aortic reconstruction during the Norwood operation, interrupted aortic arch repair with
ventral septal defect (VSD), coarctation with VSD, or cases requiring the Damus–Kaye–Stansel procedure [259,260]. These techniques are collectively referred to as regional cerebral perfusion (RCP); other terms for this technique are regional low-flow cerebral perfusion, selective cerebral perfusion, antegrade cerebral perfusion, and selective regional cerebral perfusion. Several different techniques have been described on the basis of the primary description by Pigula et al. [259]. One variation of RCP utilizes a small GoreTex graft of 3–4 mm sewn onto the innominate artery prior at initiation of CPB, and this is then used as the aortic cannula during CPB. A pre-CPB test occlusion by the surgeon of the innominate artery with bilateral rSO₂ monitoring can serve as a functional test of an intact circle of Willis. If there is a significant and reproducible decline in rSO₂ on the side of the innominate occlusion, a non-intact circle of Willis (up to 5% of neonates) is assumed and different CPB strategy (i.e., DHCA) can be planned. Other options for cannulation include a high cannulation technique of the innominate artery with a small 6- or 8-Fr. aortic cannula, which is advanced cephalad further distal into the innominate artery during RCP [261] (Figure 7.10). During aortic reconstruction, snares are placed around the brachiocephalic vessels and CPB flow is decreased, with only the brain receiving perfusion via the right carotid artery during this period. In this way, a bloodless operative field can be achieved, just as if DHCA was being performed, yet the brain is still receiving blood flow and oxygen, in theory increasing protection from hypoxic–ischemic brain injury. (Figure 7.11) Another potential advantage of this technique is seen in newborns who have extensive arterial collaterals between the proximal branches of the aorta and the lower body via the internal mammary and long thoracic arteries. In this instance, the use of RCP also provides some blood flow to the lower body, potentially protecting renal, hepatic, and GI systems from ischemic damage as well [223,262,263]. Preliminary results are promising and support the notion of improved cerebral protection [261,264], even at mild hypothermic temperatures [263,265]. Neurological monitoring has been used to aid in determining how much flow is necessary during RCP [266]. Approximately 40–50% of full flow is used (starting at 40 mL/kg/min) and adjusted according to brain saturation and/or transcranial Doppler measurements, maintaining baseline saturation in the range before the onset of RCP (90–95% range). Average flows of 50–65 mL/kg/min during RCP are required to maintain baseline cerebral blood flow velocities, rSO₂, and pressures to overcome vessel resistances and capillary opening pressures [264,267]. Flows < 40 mL/kg/min over time are unable to maintain rSO₂ greater than 40% after DHCA [268]. If the left regional saturation rSO₂ falls to more than 10% below the right, flow is increased further, assuming that the circle of Willis could be variant or incomplete, as all flow to the left cerebral hemisphere needs to traverse the circle. If a left radial arterial line or a femoral arterial line/umbilical artery catheter is in place, abdominal perfusion pressures of > 12 mmHg, correlating to radial artery pressures of 25–30 mmHg, are maintained [262].

Despite these theoretical advantages, and a study demonstrating that selective cerebral perfusion does provide oxygenated blood flow to both cerebral hemispheres [264,268], longer-term neurodevelopmental outcome studies to date have not demonstrated clear superiority of
RCP vs. DHCA for aortic arch reconstruction in neonates. Andropoulos et al. reported 12-month neurodevelopmental outcomes of a cohort of 34 neonates after RCP using the Bayley Scales of Infant Development III and found the mean cognitive score equal to the reference population norm, while the language and motor scores were both 0.8 standard deviations below norms. The study was not controlled and used the newest version of the Bayley test, preventing direct comparison with earlier studies by Goldberg (57 patients) and Visconti (29 patients), which both demonstrated no neurodevelopmental outcome difference between RCP and DHCA, with both mental and motor scores significantly lower than population norms at 12 months. Algra et al. [269] randomized 36 HLHS patients undergoing Norwood stage I operation to DHCA vs. RCP, and performed postoperative brain MRI. The overall incidence of new brain injury was significant at 76% and not different between groups, although the RCP patients were the only ones with new infarctions in deep brain structures. Significantly, RCP flow rates were higher in the Andropoulos et al. study [270] than in the other three, and theirs was also the only one to employ neurological monitoring to adjust RCP flows. Outcome studies of RCP must be interpreted with caution and the details of the technique must be assessed [263–272].

**Blood gas management: pH-stat vs. alpha-stat**

Some degree of hypothermia is utilized for nearly every cardiac operation in order to slow the metabolism and oxygen consumption of all organs, particularly the brain and heart [273]. During cooling, the carbon dioxide contained in blood becomes more soluble and its partial pressure decreases. The PaCO₂ sensed by the body therefore decreases as body temperature decreases, with the result that at a core temperature of 17–18°C, if pH and PaCO₂ have not been corrected for temperature, the body is experiencing a pH of about 7.6 and PaCO₂ of 15–18 mmHg [274] (Figure 7.12). This very low PaCO₂ causes cerebral vasodilatation, particularly during the cooling phase of bypass, which in turn leads to lower cerebral blood flow, less efficient brain cooling, and consequently less cerebral protection at a given temperature [250]. Since blood samples are heated to 37°C prior to measurement of pH, PaCO₂, and PaO₂, the use of pH-stat management necessitates that blood gases are being corrected for the patient’s actual body temperature by increasing the PaCO₂ on bypass as it is measured at 37°C, so that the body experiences a PaCO₂ of approximately 40 and a pH of 7.4 at all temperatures. Conversely, alpha-stat management means not correcting the blood gases for temperature, as if the patient’s blood was always at 37°C, with the goal of a pH of 7.4 and PaCO₂ of 40 mmHg. In the early history of CPB, pH-stat was utilized to preserve cerebral blood flow [275]. Randomized controlled studies in the 1970s and 1980s on adults undergoing CPB confirmed that acute, post-CPB neurological problems were worsened with the use of pH-stat management [276]. Alpha-stat management was therefore adopted for both adult and pediatric CPB. However, recent animal studies in a neonatal piglet model have challenged this conclusion, proving that neurological outcome, both behavioral and neuropathological, is significantly worse when alpha-stat management is used [250,251].

Advantages of pH-stat CPB have been shown to include:
- a decreased brain metabolic rate
- an increased rate of brain cooling and reperfusion [277], thereby providing better protection through more even and faster cooling and rewarming secondary to increased CBF [277,278].
- molecular effects of altered arterial PO₂ and pH, including changes in cerebral oxygenation and brain enzyme activity as well as decreased brain electrical activity [279–280].
- improved oxygen delivery through decreased oxyhemoglobin affinity [281] by counteracting the pH and hypothermia-associated leftward shift in the oxyhemoglobin dissociation curve
- increased cortical oxygenation before arrest (through hypercapnic capillary vasodilation [282]) and decreased oxygen metabolic rate providing slower deoxygenation compared to alpha-stat management (10 vs. 7 minutes) [250] (Figure 7.9). Cortical anoxia occurs at 36 vs. 24 minutes for alpha-stat management, a safety margin of 50%.

In cyanotic infants with aortopulmonary collaterals, pH-stat management results in significantly improved brain oxygenation as measured by near-infrared cerebral oximetry [283]. A retrospective study of 16 patients revealed worse neurodevelopmental outcomes with alpha-stat management [249]. In a randomized prospective trial of pH vs. alpha-stat management in 182 infants <9 months of age, there was a strong trend toward improved outcomes with pH-stat management, including earlier return of EEG activity, fewer seizures, and improved psychomotor development index [187]. Bellinger et al. [284], in their landmark study, examined the effects of alpha-stat and pH-stat on developmental and neurological outcomes after deep hypothermic CPB in infants. The Psychomotor Development Index scores of 110 patients did not differ significantly between the groups ($P = 0.97$). Bellinger et al. concluded that the use of alpha-stat or pH-stat strategy is not consistently associated with improved or impaired early neurodevelopmental outcomes in infants undergoing deep hypothermic CPB [284].

One reason for the differing results between pediatric and adult studies is that the increased cerebral blood flow produced by pH-stat management leads to a greater number of cerebral emboli in adults. Emboli occur much less frequently in children, and the primary etiology of neurological injury from CPB in pediatric patients is hypoxic–ischemic [285]. Thus, the increased cerebral blood flow observed on CPB with pH-stat management lessens this risk in children. Interestingly, this putative mechanism has been recently challenged by a study
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In vivo

Figure 7.12 pH and PCO_2 changes when blood temperature is varied between 17°C and 37°C. Point A is the starting point with pH 7.4 and PCO_2 of 40 at 37°C. Points B, C, D, and E are the conditions the brain experiences at 17°C with various blood gas management strategies. pH-stat management (correcting the pH and PCO_2 for temperature) results in an acid–base environment that is neutral, whereas α-stat management (not correcting for temperature) results in a very alkalotic environment at 17°C. Warming the blood sample (as is done for blood gas measurement) results in very high PCO_2 values when pH stat is used. The pH of blood becomes slightly more alkalotic with cooling owing to the decreased dissociation of hydrogen ions. (Source: Jonas [274]. Reproduced with permission of Taylor & Francis.)

involving a controlled microembolic load and DHCA in pigs that revealed that pH-stat was still associated with improved outcomes when compared with alpha-stat [286]. Recent studies have also revealed a decrease in peak postoperative troponin levels, reduced ventilator dependence, and reduced ICU stays with pH-stat as compared with alpha-stat [287].

Currently, the preferred technique in adults is the alpha-stat method because it is believed that cell function and autoregulation are better preserved by maintaining neutral pH according to the temperature of the cell. In pediatric cardiac surgery, however, unlike the adults, pH-stat enhances cerebral and systemic protection during DHCA. Most congenital heart surgery programs have reverted to pH-stat management. This necessitates careful attention to PaCO_2 during all phases of bypass, potentially reducing the sweep gas flow to decrease the efficiency of CO_2 removal, and often adding inspired CO_2 to the sweep gas of the bypass circuit, particularly in small infants.

**Sickle cell disease**

Sickle cell disease is an inherited hemoglobinopathy in which a mutation in the β-globin gene on chromosome 11 causes the sixth amino acid of the β-globin chain to be changed from valine to glutamic acid. The disease is inherited in an autosomal recessive pattern, with a homozygous form (Hgb SS) and a heterozygous form, or sickle cell trait (Hgb AS). The sickle cell gene is most commonly observed in African populations, with 1 in 500 African-Americans having Hgb SS, and 1 in 12 with sickle cell trait [288]. In the United States and most developed countries, there is now universal newborn screening for hemoglobinopathies, and sickle cell disease is therefore usually diagnosed at that time. After the normal postnatal decline in fetal hemoglobin (Hgb F) in the first 6 months, Hgb SS patients have Hgb S concentrations of 70–98%, and Hgb AS patients have Hgb S concentrations of 30–50%. Hgb S causes sickling of red cells, leading to chronic hemolytic anemia and impaired microvascular perfusion. This can result in end-organ dysfunction and permanent injury, including painful bony crises, splenic sequestration and autoinfarction, acute chest syndrome with hypoxemia, retinopathy, renal failure, pulmonary hypertension, and stroke. Hypoxemia, acidosis, cold temperature, hypovolemia, and microvascular stasis all promote sickling. Other less common forms of sickle cell disease are sickle cell-hemoglobin C disease (Hgb SC), and sickle cell-thalassemia variants. The reader is referred to excellent recent reviews for further detailed information about these disorders [288,289]. Modern treatment for Hgb SS now includes chronic transfusion therapy to maintain the Hgb S at < 30%, with Hgb levels of 9–10g/dL. In addition, hydroxyurea is now commonly used in sickle
cell disease because of its ability to increase production of Hgb F, reduce Hgb S, and decrease severity of disease manifestations. Hydroxyurea can substantially reduce the Hgb S percentage, and so this should be considered in the preoperative planning for these patients. The conditions commonly encountered for CPB – hypothermia, low flow, acidosis, and hypoxemia – all predispose to sickling, and a careful strategy is required to optimize outcomes in these patients [290,291]. Although no universally accepted guidelines have been published, recent data and reviews provide important guidance. Careful consultation with the patient’s hematologist and surgeon, and a clear strategy devised with the perfusionist, are essential when planning for CPB.

Exchange or straight transfusion has been used successfully for CPB surgery in sickle cell disease, either preoperatively, or in the operating room with the initiation of CPB [292,293]. Preoperative exchange transfusion is cumbersome, expensive, and usually not necessary. If preoperative straight transfusion is utilized, the goals are to achieve an Hgb of 10 g/dL, with Hgb SS < 30%. Other common approaches include a partial exchange transfusion performed at the time of initiation of CPB. CPB prime volume is increased to two to three times the patient’s blood volume, with PRBCs and colloid or crystalloid calculated to achieve a Hct of 30% and Hgb S well below 30% on CPB. In addition, 25–33% of the patient’s blood volume is diverted from the venous return upon initiation of CPB, and discarded instead of draining into the venous reservoir, further diluting Hgb S. Other recommendations for CPB are to perform the surgery at normothermia whenever possible, and to limit hypothermia to mild (≥32°C) if it is needed. [291,293]. If deeper levels of hypothermia are required, a more extensive exchange transfusion is necessary with Hgb S < 10%. In addition, frequent arterial blood gases are measured on CPB with a goal of full arterial oxygen saturation (PaO₂ >100 mmHg), and mixed venous blood gases also assessed with the goal of SvO₂ >75–80%. Maintaining full CPB flows at 2.4–3.2 L/min/m² or above, and perfusion pressures in the high normal range is also important. Finally, cardioplegia strategies may be altered, with some authors recommending only crystalloid cardioplegia, with an initial “warm” dose at 26–32°C, to wash out any red cells from the coronary arteries before cold cardioplegia is given [291,293]. As noted earlier, sickle cell trait (Hgb AS) patients may still have Hgb S concentrations of 30–50% at baseline, and, although asymptomatic under normal conditions, are at risk for sickling with CPB. Therefore, sickle trait patients should be approached in the same manner as homozygous sickle cell disease patients for CPB cases [293]. Using these CPB recommendations, Yousafi et al. reported outcomes for 21 pediatric and 26 adult patients with sickle cell disease or trait [293]. No patient had a perioperative sickling crisis; however, two patients had stroke, and two had renal failure postoperatively. Whatever the ultimate protocol for CPB management for the sickle cell patient, close vigilance in the postoperative period is critical, especially for acute chest syndrome with hypoxemia, the most common perioperative sickling complication [288]. Renal failure and stroke are also threats in the perioperative period after CPB surgery. Recommendations for sickle cell disease and CPB are summarized in Table 7.6. Published data about other hemoglobinopathies such as thalassemia are scant, and the anesthesiologist should consult with the patient’s hematologist and surgeon when planning strategies for this rare situation [289].

### Cold agglutinins

Cold agglutinin disease in pediatric patients is most commonly observed after *Mycoplasma pneumoniae* infection, in as many as 55% of patients in the first 2 weeks of this disease [291]. Antibody levels peak in the third week, and decrease significantly by 2–3 months after infection. Cold agglutinins are usually immunoglobulins of the IgM class, and are characterized by reaction at cold temperatures with surface red blood cell antigens, causing activation

<table>
<thead>
<tr>
<th>Preoperative</th>
<th>Intraoperative CPB</th>
<th>Postoperative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintain euvolemia with IV hydration</td>
<td>Partial exchange transfusion with CPB: prime volume two to three times blood volume with PRBCs; target Hct on CPB &gt; 30%; Hgb S &lt; 30%</td>
<td>Avoid hypoxemia; SpO₂ &gt; 95% at all times</td>
</tr>
<tr>
<td>Avoid hypoxemia, hypothermia, acidosis</td>
<td>Avoid hypothermic bypass, temperature &gt; 32°C if needed</td>
<td>Maintain euvolemia</td>
</tr>
<tr>
<td>Consider straight transfusion to Hgb &gt;10 g/dL and Hgb S &lt;30%</td>
<td>Warm crystalloid cardioplegia for first dose Full flow CPB at all times &gt;2.4 L/min/m²</td>
<td>Avoid hypoxemia: PaO₂ &gt; 100 mmHg</td>
</tr>
<tr>
<td>Exchange transfusion rarely indicated</td>
<td>Avoid hypoxemia: PaO₂ &gt; 100 mmHg</td>
<td>SvO₂ &gt; 75–80%</td>
</tr>
<tr>
<td></td>
<td>Avoid hypotension</td>
<td>Maintain Hgb &gt;10 g/dL and Hgb S &lt; 30%</td>
</tr>
<tr>
<td></td>
<td>Temperature corrected pH 7.35–7.45</td>
<td></td>
</tr>
</tbody>
</table>

IV, intravenous; Hgb, hemoglobin; Hct, hematocrit; PRBCs, packed red blood cells; SvO₂, mixed venous oxygen saturation; SpO₂, pulse oximeter saturation.
of the complement pathway, with agglutination and hemolysis. Reported adverse effects during hypothermic CPB include massive hemagglutination, microvascular thrombosis and hemolysis, with coronary thrombosis, inability to deliver cardioplegia, and oxygenator failure. Typically, cold agglutinin disease is characterized by high antibody levels at 4°C and low levels at normothermic temperature; however, the level of hypothermia at which agglutination occurs can vary, and when cold agglutinin disease is diagnosed preoperatively it is important to define the temperature range at risk. The true incidence of cold agglutinin disease in pediatric patients is not known, but it appears to be very low. Elective cases in the face of post-

**Leukoreduction and irradiation of blood products**

Leukoreduction of blood products (PRBCs, platelets, and whole blood) has been described in attempts to reduce the
inflammatory response to CPB from leukocyte reduction, by employing leukocyte-reducing blood filters either before or during CPB. However, in the two controlled trials in pediatric patients, there were no clinical outcome differences in leukoreduced patients [294]. More commonly, leukoreduction is performed to provide “cytomegalovirus (CMV)-safe” blood products, as this virus is contained entirely in white blood cells [295]. Leukoreduction for all units of PRBCs, platelets, and whole blood has become standard practice in many hospitals because of the high prevalence (35–65%) of seropositivity for CMV in donated blood units. Despite this practice, 0.02–0.25% of blood units still test positive for CMV, and so transmission is still possible [295]. Patients who are or who may become transplant recipients may require CMV-negative blood confirmed by donor serology; local policies vary and need to be well understood by the anesthesiologist.

Irradiation of blood products (PRBCs, platelets, FFP, whole blood) prevents graft-versus-host disease from transfused leukocytes. This is a rare but serious complication, and has resulted in uniform irradiation policies for high-risk groups, which include premature neonates and young infants in the first 3 months of life, immunosuppressed patients such as some transplant recipients, and those who have had blood donated by relatives [296,297]. Irradiation causes several changes due to hemolysis of PRBCs, including potassium release, acidosis, increased lactate, increased free hemoglobin, and decreased glucose [298]. Hyperkalemia with K⁺ levels over 20 mmol/L are common even with irradiated PRBC units less than 7 days after donation. Irradiated PRBC units should be checked for K⁺ levels, and consideration should be given to washing the units before CPB, especially in neonates.

### KEY POINTS: SPECIAL CPB MANAGEMENT ISSUES

- Warm or tepid temperatures are successfully used in pediatric cardiac surgery.
- DHCA remains a cornerstone of neuroprotection for complex cases involving aortic reconstructions, such as the Norwood procedures.
- Deep hypothermia involves complex management issues in respect of the maintenance of hematocrit, even cooling of the brain over 20 minutes using a pH-stat strategy, cold, normoxemic reperfusion, and the avoidance of hyperthermia postoperatively.
- RCP was developed in an attempt to provide continuous cerebral perfusion throughout the repair. A minimal flow of 40 mL/kg/min is required.
- To date, there is no proven superiority of one method over the other.

### Monitoring anticoagulation during and after CPB

Since the landmark 1959 paper by Keats and colleagues from Texas Children’s Hospital, heparin reversal by protamine, and its assessment using the ACT has been the standard approach for confirming anticoagulation with heparin, and reversal of the heparin by protamine [299]. The celite ACT test with a target time of 400–480 seconds has remained the standard for initiation and maintenance of anticoagulation on CPB in many institutions for over 50 years. Reversal of the heparin effect is with protamine, and return to baseline ACT serves as confirmation of neutralization of this heparin effect. ACT is a point-of-care test performed by the perfusionist on a device often mounted on the CPB machine, and its rapid turnaround is unmatched by other tests. However, the ACT is only a gross measure of the initiation of clotting, will be affected by many factors other than heparin (e.g. thrombocytopenia or platelet dysfunction), and does not measure fibrinolysis or other aspects of clot persistence (clot strength). Several other point-of-care heparin and coagulation monitors will be discussed here; the reader is referred to Chapter 13 for additional details.

Point-of-care heparin–protamine titration systems for the measurement of plasma heparin concentrations (Hepcon®, HMS Plus®; Medtronic, Inc., Minneapolis, MN, USA) perform an in vitro bedside assay to determine plasma heparin concentrations. Plasma heparin levels of 3.0 units/mL are considered adequate anticoagulation for CPB, and use of this system is effective to titrate additional heparin doses during bypass. In a study of 44 patients under the age of 6 months undergoing CPB, Guzzetta et al. compared ACT, Hepcon, and direct plasma heparin concentration using an antifactor Xa chromogenic substrate assay [300]. ACT showed no correlation with plasma heparin concentration after the initial heparin bolus or during CPB; there was modest correlation with one of the ACT methods just before termination of CPB. Hepcon demonstrated a good correlation with direct plasma heparin level measurement, as well as an acceptable bias by Bland–Altman analysis, with Factor Xa heparin levels higher by 0.49–0.67 units/mL than Hepcon heparin levels. Gautam et al. reported on 100 patients aged 1 month–5 years who had two different methods of protamine dosing compared, the first based on estimated blood volume of the patient plus CPB prime volume and the second based on patient blood volume alone [301]. Hepcon, ACT, and TEG (see later) were measured in both groups, and although protamine neutralization of heparin was successful by both methods, the authors concluded that the protamine dose calculated by Hepcon resulted in lower plasma protamine concentrations; excess protamine prolonged the clotting time (R value; see later) as measured by TEG. Therefore, heparin–protamine titration may result in more accurate maintenance of desired heparin levels during bypass, as well as avoiding excessive protamine dosing after neutralization.
Figure 7.14 Normal thromboelastography tracing. R, reaction time (in minutes until first detectable levels of fibrin clot formation). Sensitive to heparin and coagulation factor levels. Angle – reflects fibrinogen activity, but does not always correlate with direct measurements. MA, maximum amplitude – clot strength, combination of platelet count and function plus fibrinogen activity. LY30, percent clot lysis after 30 minutes – measurement of fibrinolysis. G, clot firmness in dynes/second (d/sc). (Source: Chen & Teruya [302]. Reproduced with permission of Elsevier.)

Thromboelastography (Medtronic, Inc.) and thromboelastometry (ROTEM®; TEM International GmbH, Munich, Germany) are related methods that measure clot initiation and maintenance of clot integrity and therefore provide a more complete profile of the coagulation system. TEG uses shear elasticity of a 0.36 mL blood sample, measured by the constraint of rotation of a cup and pin as fibrin strands and then a platelet-fibrin clot forms, attached to a torsion wire transduced to an electronic signal that displays a plot [302]. (Figure 7.14). Time to initiation of clot, maximum clot strength, and breakdown as a result of fibrinolysis are measured. Heparinase can be added to the sample to eliminate heparin effect, and kaolin to speed initiation of clot formation to make TEG more of a real-time point-of-care test. Despite this, a minimum of 10–15 minutes are required to acquire data about the time of initiation, and the speed of initiation of clot, and 45–60 minutes to acquire a full profile that includes fibrinolysis. Despite some data in the adult population that TEG can guide the anesthesiologist as to what blood product (platelets, FFP, cryoprecipitate) and what dose to administer, in pediatric cardiac surgery this degree of real-time utility has not been demonstrated. Recent TEG studies have demonstrated that the method is sensitive to reduced platelet number and fibrinogen concentration, and that these parameters, especially maximum amplitude, correlated well with post-bypass bleeding [303]. Platelet count < 120,000/L and fibrinogen concentration of < 100 mg/dL were predictive of bleeding and abnormal TEG results.

Thromboelastometry (ROTEM) is similar to TEG in that a small blood sample in a cup is rotated around a pin, but instead of a torsion wire, the formation of clot (constraint of rotation of cup) is detected by an optical light-emitting diode detection system. This feature, and better fixation of the rotating pin, may make ROTEM more resistant to vibration and small movements, to make it more suitable for point-of-care testing in the operating room. The ROTEM tracing and parameters are similar to TEG (Figure 7.15) [304]. In addition to heparinase, cytochalasin D can be added to the test to discern fibrin polymerization early, with clot strength at 10 minutes having strong correlation to clot strength at 30 minutes ($r = 0.91–0.97, P < 0.001$) [305]. This allows the test to be done during CPB with results that can be interpreted after about 15 minutes. The post-bypass ROTEM maximum clot firmness parameter correlated with bleeding in one small study [306]. A comparison of TEG and ROTEM parameters is given in Table 7.7 [307].

Because platelet defects, both in number and function due to activation from the bypass components and procedure, are the most common and serious cause of post-bypass coagulopathy in young infants [308], point-of-care platelet function tests have been proposed to guide administration of platelets (Sonoclot®, Sienco, Inc., Boulder CO, USA; TEG PlateletMapping®, Medtronic, Inc.). Data are very limited in pediatric cardiac surgery, and to date these tests cannot be recommended as part of routine care [309,310].

Each institution must develop an approach to monitoring of coagulation for CPB cases to reduce unnecessary blood transfusion while achieving prompt hemostasis, and avoiding inappropriate protamine dosing, particularly for neonatal and other complex cases at high bleeding risk. The available evidence suggests that a heparin–protamine titration system to ensure accurate heparin dosing and reversal, combined with a point-of-care clot formation and integrity test such as TEG or ROTEM, may be best able to achieve this [311]. Whatever the testing regimen, recent data have confirmed the classical papers demonstrating that platelets are the primary defect, followed by hypofibrinogenemia, in complex cardiac surgery in infants [312].
Figure 7.15 Normal ROTEM® tracing. (Source: http://www.rotem.de/site/ Reproduced with permission of Tem International GmbH.)

Table 7.7 Variables measured by the thromboelastography (TEG®) and ROTEM®

<table>
<thead>
<tr>
<th>Variable</th>
<th>TEG</th>
<th>ROTEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measurement period</td>
<td>–</td>
<td>Reaction time (RT)</td>
</tr>
<tr>
<td>Time from start to when the waveform reaches 2 mm above baseline</td>
<td>R</td>
<td>Clotting time (CT)</td>
</tr>
<tr>
<td>Time from 2 mm above baseline to 20 mm above baseline</td>
<td>K</td>
<td>Clot formation time (CFT)</td>
</tr>
<tr>
<td>Alpha angle (°)</td>
<td>α (slope between R and K)</td>
<td>α (angle of tangent at 2 mm amplitude)</td>
</tr>
<tr>
<td>Maximum angle</td>
<td>–</td>
<td>CRF</td>
</tr>
<tr>
<td>Maximum strength</td>
<td>Maximal amplitude (MA)</td>
<td>Maximal clot firmness (MCF)</td>
</tr>
<tr>
<td>Time to maximum strength</td>
<td>–</td>
<td>MCF-t</td>
</tr>
<tr>
<td>Amplitude at a specific time</td>
<td>A30, A60</td>
<td>A5, A10</td>
</tr>
<tr>
<td>Clot elasticity</td>
<td>G</td>
<td>MCE</td>
</tr>
<tr>
<td>Maximum lysis</td>
<td>–</td>
<td>CLF</td>
</tr>
<tr>
<td>Clot lysis (CL) at a specific time (min)</td>
<td>CL30, CL60</td>
<td>LY30, LY45, LY60</td>
</tr>
<tr>
<td>Time to lysis</td>
<td>2 mm from MA</td>
<td>CLF (10% difference from MCF)</td>
</tr>
</tbody>
</table>

MCE, maximal clot elasticity; CLT, clot lysis time; CLF, clot lysis fraction.

**KEY POINTS: MONITORING ANTICOAGULATION DURING AND AFTER CPB**

- For over 50 years the standard method has been heparin administration and protamine neutralization monitored by ACT.
- Heparin–protamine titration systems allow for more accurate heparin and protamine dosing.
- TEG and thromboelastometry allow more accurate blood product administration after bypass.

**Complications and safety**

The most frequent causes of death or injury related to CPB mishaps have been arterial embolism and consumptive coagulopathies. Other life-threatening events include thrombus in the extracorporeal circuit, inadequate pressures and flows, aortic dissections, separation of extracorporeal lines, drug administration errors, protamine administration during CPB, heparin overdose, transfusion reactions, negative pressure complications (principally air entrainment), electrical failure, and failure to provide gas exchange. The incidence of fatal accidents in recent surveys of adult and pediatric perfusion is in the range of 1 in 1,300 to 1 in 4,900 procedures. Serious or permanent injury is reported in 1 in 1,139 to 1 in 2,500 cases. Near misses or incidents occur in approximately 1 in 138 to 1 in 198 cases. [313–315]. Pre-bypass checklists, vigilance on the part of all members of the team, and the use of standard perfusion monitors and devices will minimize catastrophes.

The most common problems in pediatric practice are inadequate pressures or flow from either poor venous return (most often due to cannula placement) or problems at the arterial cannulation site (malposition of the aortic cannula, e.g., in the innominate artery with preferential perfusion of the right carotid; dissection or hematoma).

Most situations can be controlled by rapid recognition, correction or – in rare cases – separation from bypass and...
restoration of normal circulation, unless the aorta has been ruptured. A great deal of suspicion and good communication amongst the team are vital in this respect.

Conclusions and future perspectives

In summary, pediatric CPB is challenging as it extends the spectrum of extracorporeal circulation in many aspects. Familiarity with differences to adult bypass circuits and management is of the utmost importance and the team, consisting of cardiac surgeon, perfusionist, and anesthesiologist, has to work very closely together to reach the goal of good perfusion practice. The results of this hard work are rewarding, however, and offer many children a better perspective and greater life expectancy. There are myriad variations in bypass technique, specific to each institution and often to each individual surgeon within an institution. No one technique has been conclusively proven to be superior to others with regard to myocardial and clinical outcomes; better neurological outcomes have been demonstrated with avoidance of extreme hemodilution and prolonged DHCA. Future directions lead towards a “goal-directed perfusion management” with special emphasis on organ protection and further technical advances in miniaturization of the CPB circuit size to reduce the use of blood transfusions and the inflammatory response. Together with the determination of a safe Hct limit, this may render the asanguineous neonatal CPB possible. A checklist approach is useful in developing the individual anesthesiologist’s approach to CPB in children (see Table 7.6).

Selected references

A full reference list for this chapter is available at:
http://www.wiley.com/go/andropoulos/congenitalheart


Organs 2005;29:876–9. Report of a randomized trial comparing end-of-bypass rectal temperature of 35.5°C or 37.0°C in 50 pediatric patients. No after-drop in temperatures was observed in either group. There were no between-group differences in temperatures measured out to 16 hours postoperatively, no shivering, and no differences in heart rate and blood pressure. Given the potential adverse effects of elevated brain temperature after bypass, there is no reason to rewarm pediatric patients above 35.5°C to prevent afterdrop.


245 Wypij D, Newburger JW, Rappaport LA. The effect of duration of deep hypothermic circulatory arrest in infant heart surgery on late neurodevelopment: the Boston Circulatory Arrest Trial. J Thorac Cardiovasc Surg 2003;126:1397–403. The classic article demonstrating that prolonged circulatory arrest over about 41 minutes is associated with lower neurodevelopmental scores at age 4 years after the neonatal arterial switch operation.


CHAPTER 8

Multiorgan Effects of Congenital Cardiac Surgery

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Introduction

The diagnosis and surgical management of congenital cardiac disease in the pediatric patient present a profound challenge to a developmentally immature physiology. Associated congenital syndromes, chronic abnormalities in hemodynamics, and immature developmental physiology of the young child all result in the potential for multisystem aberration. The exposure of a patient in this relatively tenuous state to the systemic challenges associated with cardiopulmonary bypass (CPB) result in both short- and long-term challenges in the management of these children.

The systemic inflammatory response and congenital cardiac surgery

Cardiopulmonary bypass triggers a complex cascade of cellular and humoral inflammatory responses designed to respond to noxious stimuli. Children are particularly prone to the effects of this response, due to the large surface area of bypass circuit relative to blood volume, a child’s increased metabolic demand requiring higher flow rate while on CPB, and developing organ systems that are particularly prone to injury. These inflammatory consequences of CPB predispose the pediatric patient to end-organ dysfunction and multisystem organ failure.

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(MSOF). The management of this end-organ dysfunction, which includes coagulopathy, pulmonary and myocardial dysfunction, renal insufficiency, and diffuse capillary leak, represents a major challenge in the immediate postoperative management.

Activation of complement, the kinin–kallikrein–bradykinin system, the coagulation system, and fibrinolysis results in a systemic response that is both highly redundant and self-amplifying due to the presence of multiple positive feedback loops. These events are triggered immediately upon contact of the patient’s blood with the foreign surfaces of the CPB circuit. Further activation occurs as a result of mechanical shear stress on blood components, hypotension, non-pulsatile perfusion, hypothermia, intestinal hypoperfusion, and systemic reperfusion following release of the aortic cross-clamp. Additionally, administration of heparin and protamine during the course of cardiac surgery results in an increase in cellular and humoral processes that contribute to systemic inflammation and end-organ injury [1].

The response to CPB is mediated by various cytokines which facilitate communication between components of the immune and inflammatory systems. They are polypeptide hormones of low molecular weight (5–20 kD) produced by macrophages, monocytes, lymphocytes, fibroblasts, and endothelial cells. They modulate humoral and cellular immunity in addition to the maturation and activation of immune cells. The plasma concentration of cytokines at baseline is in picomolar concentrations (10^{-12}) and may increase up to 1000-fold in the setting of injury or infection. Data regarding the degree of cytokine release following CPB, and the ratio of pro- versus anti-inflammatory cytokines, are often conflicting, owing to inconsistencies in the source, technique, and timing of sampling. It is clear, however, that identifiable waves of cytokine release characterize the inflammatory response to CPB, and that important clinical and laboratory consequences of this response are observable in the perioperative period. Additionally, the functions of individual cytokines are highly redundant and pleiotropic, which presents a significant challenge to those looking to reduce their downstream effects for clinical benefit (Table 8.1).

**Systems mediating the systemic inflammatory response to CPB**

**Complement pathway activation**

Exposure of blood to the components of the CPB circuit results in rapid activation of complement via the alternate pathway, and initiates inflammation. While this component of the complement system is designed to respond to microbial cell surface components and mediate the body’s defense against microorganisms, it may also be activated by exposure of blood to foreign surfaces, endotoxin, and kallikrein [2]. This activation results in conversion of C5 and C3 to C5a and C3a, respectively (Figure 8.1). C3a and C5a are potent anaphylatoxins which activate and degranulate neutrophils and mast cells, and initiate platelet aggregation. C5a and C3a also act directly on endothelium, producing increased vascular permeability and smooth muscle contraction. C5a primes monocytes and macrophages to greatly increase production of tumor necrosis factor-alpha (TNF-alpha) in the presence of endotoxin. This initial increase in TNF-alpha may represent an early central event in the upregulation of the systemic inflammatory response [3].

These processes (C5a and C3a activation, TNF-alpha production) result in successive surges in humoral mediators of the inflammatory response: toxic oxygen metabolites, pro-inflammatory cytokines (IL-1, TNF-alpha, IL-6, IL-8 and LPS), and anti-inflammatory cytokines which limit systemic inflammation (IL4, IL10). TNF-alpha levels increase dramatically following initiation of CPB and peak at 2 hours and 18–24 hours postoperatively [4] (Figure 8.2). Levels of C5a and C3a are directly related to the duration of CPB, and infants exhibit a more dramatic increase than neonates [5]. Attempts to correlate clinical outcomes with the degree of complement activation (using C3a and C5a plasma levels as markers) have led to inconsistent results [6,7].

In addition to the activation of the alternate complement pathway by contact with foreign surfaces, the classical complement pathway further contributes to the systemic inflammatory response when activated by heparin–protamine complexes. Their presence results in generation of C4a, and further increases in C3a production, resulting in increasing vascular permeability.

**The kinin–kallikrein system**

Kinins are polypeptides generated from kininogens following tissue injury or noxious stimulation. Their functions are incompletely understood, but are known to be involved in blood pressure regulation and mediation of inflammation through activation of G-protein-coupled B1 and B2 receptors. Kinins are potent vasodilators, which also increase vascular permeability, smooth muscle contraction and neutrophil chemotaxis. While B2 receptors are constitutively expressed in most tissues, B1 receptors are induced and functionally expressed in the presence of inflammatory cytokines, endotoxin, and following tissue injury. The generation of kinins depends upon the contact of blood with the negatively charged surfaces of the CPB circuit and subsequent activation of factor XII to XIIa. Factor XIIa results in the production of kallikrein from prekallikrein, which then results in further activation of factor XII and the production of bradykinin. This positive feedback loop amplifies the production of bradykinin, a potent mediator of both acute and chronic inflammation (Figure 8.3). Bradykinin, in turn, results in further generation of inflammatory cytokines, nitric oxide, and tissue-plasminogen activator.

**Activation of coagulation-fibrinolytic cascade**

Cardiopulmonary bypass is highly pro-coagulant. In addition to activation of the kinin system, factor XIIa...
Table 8.1 Mediators of the inflammatory response to cardiopulmonary bypass (CPB)

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Produced by</th>
<th>Target</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradykinin</td>
<td>Kinin-kallikrein system – formed from high-molecular-weight kininogen (HMWK)</td>
<td>Smooth muscle</td>
<td>Vasodilator</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Increases vascular permeability</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Contraction of smooth muscle in the bronchus and gastrointestinal tract</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Neutrophil recruitment via endothelial B1 receptor pathway</td>
</tr>
<tr>
<td>C3a</td>
<td>Alternate pathway: spontaneous hydrolysis of C3</td>
<td>Mast cells, Neutrophils</td>
<td>Stimulates mast cell degranulation</td>
</tr>
<tr>
<td></td>
<td>Classical Pathway: cleavage by C3 convertase</td>
<td>Endothelial cells</td>
<td>Activation and degranulation of neutrophils</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Chemotaxis of neutrophils (less potent than C5a)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Initiate platelet aggregation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Increased vascular permeability</td>
</tr>
<tr>
<td>C5a</td>
<td>Formed by cleavage of complement component C5 by C5 convertase</td>
<td>Mast cells, Neutrophils</td>
<td>Potent stimulator of neutrophil chemotaxis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Endothelial cells</td>
<td>Stimulates mast cell degranulation</td>
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<td></td>
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<td></td>
<td>Activation and degranulation of neutrophils</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Neutrophil sequestration in pulmonary tissue</td>
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<td>TNF-alpha production in the presence of endotoxin</td>
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<td>IL-4</td>
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<td>Lymphocytes, Macrophages</td>
<td>Lymphocyte proliferation</td>
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<td>IL-6</td>
<td>Macrophages, Endothelial Cells</td>
<td>Lymphocytes, Hepatocytes</td>
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<td>IL-8</td>
<td>Macrophages, Endothelial cells</td>
<td>Neutrophils</td>
<td>Stimulation of acute-phase reactant production</td>
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<td>IL-10</td>
<td>Macrophages</td>
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<td>Inhibits synthesis of proinflammatory cytokines</td>
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<td>Tumor necrosis factor-alpha (TNF-alpha)</td>
<td>Macrophages/monocytes</td>
<td>Endothelial cells, Neutrophils</td>
<td>Activates vascular endothelium, increases expression of adhesion molecules and increases permeability</td>
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produces diffuse activation of coagulation; this is one of the mechanisms by which the inflammatory and coagulation systems are interdependent (Figure 8.4). While heparin inhibits formation of new clot, it does not reduce the expression of tissue factor (TF) on the endothelial cells and monocytes. The interaction of TF with factor VIIa results in widespread stimulation of the coagulation cascade and the generation of thrombin, despite high circulating levels of heparin. Thrombin then perpetuates both inflammatory and thrombotic processes. Thrombin increases neutrophil adherence to endothelium and stimulates neutrophil release of chemotactic and inflammatory cytokines. Thrombin levels are elevated within minutes of the initiation of CPB, as are levels of plasminogen activator inhibitor (PAI). This prothrombotic state may persist for several hours postoperatively, even in the setting of clinical bleeding. In infants, there may be ongoing stimulus for TF expression that extends into the postoperative period [8].

Endotoxemia
Cardiopulmonary bypass decreases gastric mucosal pH and intestinal perfusion, with a subsequent increase in intestinal permeability. Endothelial dysfunction decreases the release of vasodilatory nitric oxide and prostacyclin, increasing the vascular resistance in splanchnic beds. The resulting intestinal hypoperfusion allows translocation of predominantly Gram-negative bacteria. Endotoxin, the lipopolysaccharide [9] component of the bacteria outer cell membrane, binds macrophages and monocytes, and triggers further release of inflammatory mediators. Endotoxin is present in the circulation of 96% of children following CPB.

Endotoxin is a recognized harbinger of inflammation in the setting of enteric pathology. Circulating endotoxin and inflammatory mediators (interleukin-1 [IL-1], IL-1β, and IL-8) correlate with the severity of necrotizing enterocolitis in newborns [10]. Children with greater endotoxin burden have higher serum levels of IL-6, more hemodynamic
Figure 8.1 Overview of the complement system in the setting of cardiopulmonary bypass (CPB).

Figure 8.2 Proinflammatory and anti-inflammatory cytokine responses to cardiopulmonary bypass (CPB) in children. IL, interleukin; MUF, modified ultrafiltration; TNF-alpha, tumor necrosis factor alpha. (Source: Chew et al. [3]. Reproduced with permission of Lippincott, Williams & Wilkins.)
Figure 8.3 Overview of the kinin–kallikrein system in the setting of cardiopulmonary bypass (CPB).

Figure 8.4 Overview of coagulation system in the setting of cardiopulmonary bypass (CPB).
instability, and greater mortality [11]. Data suggest that milrinone may improve gastrointestinal blood flow, and thereby reduce endotoxia and IL-6 levels in adults undergoing CPB [12]. Additionally, lower temperature during CPB has been associated with increased levels of endotoxin when compared with mildly hypothermic conditions [13].

**Final common injury pathways**
Activation of these complex inflammatory and injury cascades results in endothelial injury, microcirculatory dysfunction, and neutrophil activation.

**Endothelial injury**
Normal endothelium is an important custodian of its neighboring smooth muscle, producing vasoactive mediators such as nitric oxide and prostacyclin, which fine-tune microcirculatory function. Injury to this critical monolayer decreases production of these vasodilatory mediators, and increases release of vasoconstrictors endothelin and thromboxane A2 [14]. Endothelin probably mediates increased pulmonary vascular resistance (PVR), as higher plasma levels are found in patients who develop pulmonary hypertension. High circulating endothelin is also associated with postoperative renal dysfunction. In a swine model of renal injury following CPB, an endothelin-1 receptor antagonist reversed many changes associated with endothelial dysfunction and renal injury [15]. Altered microcirculatory function increases vascular resistance in cerebral, pulmonary, and splanchnic vascular beds, and this effect is more pronounced in hypothermia. The pulmonary endothelium, in particular, is responsible for the breakdown of several potent vasoconstrictors: angiotensin, catecholamines, and eicosanoids. Its injury therefore results in sustained increases in PVR following CPB. Endothelial dysfunction results in increases in capillary permeability and interstitial edema in addition to microcirculatory dysfunction.

**Platelet activation**
Platelets normally circulate in their quiescent, inactivated state, surrounded by intact, healthy endothelium. Prostacyclin released by normal endothelium supports this state by keeping platelets deactivated. Following CPB, with subsequent endothelial dysfunction and thrombin generation, platelets become activated and assume a spherical shape, while cytoplasmic granules extrude their contents (Figure 8.5). Glycoproteins contained in these granule membranes become expressed on the platelet surface. Released factors include platelet factor-4, beta-thromboglobulin, and von Willebrand factor from alpha granules, while the platelet surface expresses adhesion molecules, such as P-selectin, and generates phospholipid capable of supporting coagulation elements [16].

Platelet activation and adhesion to endothelium result in additional expression of endothelial transmembrane receptors which mediate binding and transmigration of activated neutrophils. This results in additional recruitment of neutrophils to the extravascular space. Clinical efforts to reduce the contribution of platelet activation to the amplification of the inflammatory response have focused on reducing shear stress on platelets, membrane oxygenators to reduce particulate microemboli, and heparin-bonded circuits.

**Neutrophil activation and sequestration**
Neutrophil activation plays a pivotal role in ischemia–reperfusion injury and destruction of the extracellular endothelial cell matrix. CPB produces widespread activation of neutrophils and increased expression of adhesion molecules on neutrophils and endothelium.

Activated neutrophils must first adhere to endothelium, and migrate across inter-endothelial junctions to produce their effects in subendothelial tissues. Selectins, integrins, and immunoglobulins mediate neutrophil adhesion, diapedesis, migration, and chemotaxis (Figure 8.6). Plasma concentrations of soluble adhesion molecules increase significantly following CPB in children with cyanosis, with longer bypass runs producing higher plasma levels [17]. Notably, E-selectin expression increases substantially following CPB in pediatric patients [16]. Additionally, IL-1 and TNF-alpha result in increased endothelial leukocyte adhesion molecule-1 (ELAM-1) expression on endothelium, facilitating further the binding of neutrophils to the endothelium. IL-1, TNF-alpha, C5a, and endotoxin all produce increased expression of immunoglobulins on endothelium and intercellular adhesion molecules (ICAM-1 and ICAM-2) on neutrophils. Additionally, IL-8 promotes interaction of activated neutrophils with endothelial ICAM-1 receptors and results in further neutrophil migration to the extravascular space.

Neutrophil adhesion and migration are followed by basement membrane destruction and further neutrophil migration into tissue. Release of proteolytic enzymes (proteases, elastases, arachidonic acid metabolites and
toxic oxygen radicals) results in damage to extravascular tissue beds, and plasma levels of these destructive enzymes are elevated following CPB. Neutrophil elastase exacerbates endothelial cell injury and increased capillary permeability, resulting in edema and organ dysfunction. Integrins CD-18 (β subunit), CD-11a, CD11b, and CD11c (α subunits) facilitate neutrophil adhesion to other cells; their upregulation is a cardinal event in the neutrophil-mediated injury to myocardium and lung following CPB. Neutrophil-mediated tissue injury is particularly apparent in pulmonary tissue, presumably because of its high degree of vascularity, and results in increased PVR and impaired endothelial-mediated pulmonary vasodilatation.

Beta-adrenergic receptor downregulation
Another systemic manifestation of inflammatory injury is decreased expression and sensitivity of β-adrenergic receptor in the myocardium and pulmonary vascular beds. TNF-alpha decreases receptor density and sensitivity to agonists following CPB [17] Additionally, TNF-alpha has direct myocardial depressant effects, possibly mediated by nitric oxide synthase (NOS) [18]. This myocardial depressant effect is dose-dependent, exacerbated by L-arginine and inhibited by NOS inhibitors [19]. These effects are often of great consequence during separation from CPB, when myocardial function is additionally impaired by a period of ischemia, and inotropic support is expected.

Mitigating the deleterious inflammatory effects of CPB
It has long been the strategy to develop effective means of mitigating the deleterious effects of the systemic inflammatory response following CPB in children. Biocoating of CPB circuits was originally proposed for this purpose in the 1960s. Since then, practices for reducing inflammation have included perioperative corticosteroids, modified ultrafiltration (MUF), and biocoating of CPB circuitry. Although many such strategies achieve reductions in the levels of inflammatory markers, studies demonstrating improvement in clinical outcomes show mixed results. Two methods commonly in use include perioperative glucocorticoids and MUF. It is clear that the challenge of effective modulation of the systemic inflammatory response to CPB in clinically meaningful ways remains elusive.

Corticosteroids
Perioperative corticosteroids are often intended to reduce the systemic inflammatory response and its deleterious effects. Corticosteroids act through nuclear transcription factors, whose binding to promoter regions decreases expression of proinflammatory mediators. While studies have demonstrated reductions in inflammatory mediator expression, there is little consensus regarding the clinical benefits of steroid administration in this setting. There is tremendous variation in the dosing regimens reported in various studies, and sample sizes are often small. Steroids administered preoperatively (8 and 1.5 hours prior to surgery) are perceived to have a greater impact on reduction of inflammation than steroids administered as part of the CPB prime, based on data obtained in a piglet CPB model [20]. However, a prospective randomized trial comparing a two-dose or single-dose regimen of methylprednisolone (30 mg/kg) found no decrease in rates of low cardiac output syndrome (LCOS) or death at 36 hours. While the two-dose regimen reduced preoperative IL-6 levels, there was no difference in inotropic requirement, duration of mechanical ventilation, intensive care unit (ICU) or hospital length of stay, or postoperative markers of inflammation [21]. The two-dose regimen was also associated with markers of renal injury [22].
A recent analysis of data from the Pediatric Health Information Systems (PHIS) and Society of Thoracic Surgeons Congenital Heart Surgery (STS-CHSD) databases reported results from 30 pediatric cardiac centers across the US from 2004 to 2008, comparing outcomes of neonates receiving methyprednisolone on the day prior to or the day of surgery. The study population included 3,180 neonates from 25 centers. They found no difference in mortality or length of hospital or ICU stay between the methylprednisolone and control groups [23].

Recent data regarding the lack of clinical effectiveness of perioperative steroids are leading many centers to reconsider their routine use [24]. In 2010, Allan et al. reviewed plasma CRP, IL-6, IL-8, IL-10, TNF-alpha, and IL-1β levels in 88 neonates undergoing biventricular repair to test the hypothesis that inflammatory mediator production is related to impaired clinical outcome [25]. Infants were not given preoperative steroids, but methylprednisolone 30mg/kg was included in the bypass pump prime. Aprotinin was used in 13% of these patients and found to have no significant impact on levels of inflammatory mediators. Adjusting for patient age and diagnostic group, investigators found a significant association between IL-6 and IL-8 levels (immediately after bypass) and ICU length of stay. The authors note that this association was of modest clinical significance in that only 4–9% of the clinical variability in ICU and hospital length of stay were attributable to differences in inflammatory mediator concentrations.

Modified ultrafiltration

Hypothermia, hemodilution, and the profound inflammatory response to CPB result in widespread capillary leak and increase in total body water. Dilution of plasma proteins, particularly in the smallest patients, results in further increases in interstitial fluid. Management of total body fluid overload can be especially challenging in the postoperative period due to concomitant myocardial dysfunction and renal immaturity often seen in the pediatric patient. MUF removes water, low-molecular-weight solutes, and inflammatory mediators via filtration immediately following CPB. Consequently, MUF reduces total body water, decreases transfusion requirement, and reduces postoperative coagulopathy [26]. It also allows return of the contents of the CPB circuit to the patient in a concentrated form [27]. MUF has been shown in an animal model (piglet) to attenuate pulmonary-derived inflammatory markers (based on reductions in IL-6 and IL-8 concentrations obtained by bronchoalveolar lavage) seen following bypass. In this model, MUF reduced PVR [28]. MUF has been shown to be effective in reducing weight gain during CPB, decreasing levels of activated complement C3a and C5a, and reducing concentrations of proinflammatory cytokines [29]. While some studies have shown little appreciable difference in levels of inflammatory mediators following MUF, others have shown increases in plasma concentrations of IL-6, IL-8 and neutrophil elastase [30].

A 2011 survey of international pediatric perfusion practice found that 71% of centers reported using some form of MUF [31]. While the clinical outcome differences associated with MUF for all patient groups are not dramatic, the beneficial effects of MUF may be more easily demonstrated in neonatal patients requiring a longer duration of CPB [32]. MUF is discussed in further detail later in the chapter.

Serine protease inhibitors

Serine protease inhibitors are a class of drugs whose primary role is inhibition of various signaling pathways. Aprotinin, originally marketed as a kallikrein and plasmin inhibitor, decreases transfusion requirements following CPB, but also has substantial anti-inflammatory effects [33,34]. Two randomized trials have shown decreased hospital stay and cost associated with aprotinin [35, 36]. Another blinded, controlled, randomized, prospective trial in 60 children under 10 kg reported decreased ventilator time [37]. Both aprotinin and tranexemic acid (not a serine protease inhibitor) reduce expression of proinflammatory genes and increase expression of anti-inflammatory proteins [38].

Since 2006, aprotinin use has severely declined and aprotinin is now unavailable in many countries, including the US. The departure of aprotinin has been driven mostly by epidemiologic evidence of renal failure in adults [39–42]. Whether the same risk transfers to the pediatric population is unclear: three recent retrospective studies have not identified aprotinin as an independent risk factor for perioperative renal failure in children [43–45]. However, another retrospective pediatric study reported an association between aprotinin and perioperative renal failure when compared with aminocaproic acid, after controlling for confounding variables [46].

Heparin-bonded circuits

Efforts to improve CPB circuit biocompatibility are often anticipated to decrease activation of cellular and humoral inflammation, and attenuate end-organ injury associated with CPB. Although the initial rationale for heparin coating of CPB circuitry was related to the antithrombotic effects of heparin, the use of heparin-bonded CPB circuit components has reduced complement activation, contact pathway activation, and cytokine production. Heparin-bonded circuits appear to adsorb lipoproteins, which may create a circuit surface that approximates that of cell membranes [47]. Heparin-bonded circuits decrease complement activation during CPB and reduce some cytokine levels, including a 51% reduction in IL-8 concentrations after CPB in children. This same small randomized controlled trial also reported that heparin-bonded circuits improved coagulation and pulmonary function.
While coated circuits have resulted in decreased complement activation and cytokine generation, the evidence regarding the ability of these circuits to reduce thrombin generation is conflicting. Cardiotomy suction significantly increases thrombin generation, and neutrophil and platelet activation; and contribution of this major perturbation may account for some of this ambiguity [48]. Although definitive data on clinical outcomes in children regarding heparin-bonded circuits are lacking, adult data suggest that heparin-bonded circuits are associated with reduction in red blood cell transfusion, re-sternotomy, duration of mechanical ventilation, ICU length of stay, and inflammatory response following CPB [49,50]. The clinical impact of heparin-bonded circuits in children warrants further study, particularly in high-risk patients.

**Transfusion and inflammation**

Transfusion alone appears to exacerbate the systemic inflammation of cardiac surgery. Transfusion following cardiac surgery is associated with various markers of inflammation [51], and with clinical outcomes such as longer ventilator times [52–54]. Univariate analyses show that red cell transfusion is associated with nearly every complication of congenital heart surgery, and transfusion is strongly associated with infectious complications, after controlling for confounding variables in a propensity analysis [55]. Authors have argued that transfusion-related immunologic responses alone are good reasons to optimize transfusion management [53,54,56].

While transfusion is frequently required in children in order to maintain adequate oxygen delivery, efforts should be made to reduce the volume of transfusion required. Reduction in transfusion requires a multimodal intervention, necessitating diligence, cooperation, and close communication among surgical, anesthesia and perfusion personnel. Meticulous hemostasis, reduction in transfusion requires a multimodal approach, that heparin-bonded circuits are associated with reduction in red blood cell transfusion, re-sternotomy, duration of mechanical ventilation, ICU length of stay, and inflammatory response following CPB [49,50]. The clinical impact of heparin-bonded circuits in children warrants further study, particularly in high-risk patients.

**Effects of congenital heart surgery on coagulation, hemostasis, and thrombosis**

**Disturbances in the coagulation system in pediatric cardiac surgery**

Hemorrhagic and thrombotic complications of pediatric cardiac surgery represent causes of significant morbidity, and increase in both severity and frequency with decreasing age of the child [58–62]. Infants under 1 year of age experience average blood losses within the first 24 hours after surgery of 40 mL/kg, about half of the patient’s blood volume [62]. Thrombosis is also common in children with congenital heart disease (CHD), and is associated with significant morbidity [63–67]. Venous thrombosis in children is a potentially devastating complication of congenital heart surgery, and is reported to occur in as many as 16% of cases [68–70]. Central venous thrombosis and massive thrombotic disease in multiple organs occur with highest frequency in the youngest children and can yield catastrophic sequelae [71–73].

**Unique aspects of pediatric coagulation**

The hemostatic system of young children differs significantly from that of adults [74]. Healthy infants exhibit levels of the contact factors (factors XII and XI, high-molecular-weight kininogen, prekallikrein) that are 40–50% of adult levels at birth, and approach adult levels by 6 months of age. This profile is also followed by the vitamin K-dependent factors (II, VII, IX, and X) [74–77]. Factors V, VIII, and von Willebrand factor reach adult levels more rapidly, and, as is the case for von Willebrand factor, can exceed adult levels. Coagulation factor II, VIII, IX, and X all follow the pattern of the contact and vitamin K-dependent factors [74].

Fibrinogen and plasminogen, although present at nearly adult levels in the term newborn, exist in forms that differ in their post-translational modification [78,79]. A fetal fibrinogen peptide, Fib-420, is present at higher levels in neonates than in older children and adults, and is characterized by an extended alpha chain [80]. The specific...
function served by Fib-420 in fetal and neonatal physiology is unclear, but it may serve a thromboprotective role [79].

Hemostasis in CHD
Congenital heart disease imposes additional modifications on pediatric hemostasis. In cyanotic children, polycythemia further dilutes coagulation factors. Decreased levels of factors V, VII, and VIII, increased fibrinolysis, thrombocytopenia and abnormal platelet function are frequently present, and correlate with the degree of cyanosis [81]. Children with CHD have an increased incidence of heritable coagulopathies [82,83], combined deficiencies or partial deficiencies of factors VIII, XI, and XII [84], and loss of high-molecular-weight von Willebrand factor multimers [85]. Procoagulant abnormalities in cyanotic patients are partially normalized by completion of cavopulmonary anastomosis in the Fontan operation [170], but post-Fontan patients still exhibit abnormalities consistent with endothelial dysfunction and ongoing coagulation activation [86]. Factor deficiencies or partial deficiencies following the Fontan operation appear to follow a distinct ethnic pattern [87].

Pediatric patients and CPB
Children also differ from adults in their response to CPB [58,88–90]. Because of the large relative pump prime volume, hemodilution is a greater cause of decreased factor levels after CPB [90]. Thrombin activation occurs during CPB and contributes to further consumption of coagulation factors. Hypofibrinogenemia and residual heparin are common causes of post-CPB coagulopathy in children [91].

Unlike adults, most children do not exhibit pronounced fibrinolytic activity after CPB [61,73], and consequently efforts to reduce bleeding by the use of antifibrinolytic drugs are usually less effective in children than in adults [36,92–96]. Fibrinolysis also does not correlate with blood loss or transfusion in children [61]. Furthermore, platelets of young infants are generally less reactive than those of older children and adults, and decreased platelet activation, as measured by changes in adhesive receptor density, has been observed following CPB in infants [73].

Risk factors for hemorrhagic complications in pediatric cardiac surgery
Numerous studies have identified clinical risk factors for hemostatic complications after pediatric cardiac surgery. In their classic study of over 500 pediatric patients, Williams et al. found that postoperative bleeding is associated with higher hematocrit, complex surgery, lower platelet count and duration of circulatory arrest, but younger age was the most significant contributor [97]. Other multivariate analyses have revealed that younger age, hypothermia, surgical complexity, high preoperative hematocrit, and low platelet count were highly correlated with blood loss and transfusion [59,62,97–99]. Box 8.1 summarizes coagulation system changes and pediatric cardiac surgery.

Box 8.1: Coagulation system and cardiac surgery

- Coagulation system of infants and children is unique
  - Lower levels of many factors
  - Expression of differently processed forms of some factors
- Congenital heart disease imposes changes on coagulation system:
  - Frequent concurrent deficiencies of many factors
  - Cyanosis-induced decreases in factors V, VII, and VIII
  - Increased fibrinolysis
  - Low-grade disseminated intravascular coagulation (DIC)
  - Decreased platelet number and function
- Cardiac surgery imposes changes on the coagulation system of children:
  - Hemodilution
  - Fibrinolysis
  - Platelet dysfunction
  - Thrombin generation and factor consumption

Optimization of transfusion management in pediatric cardiac surgery

Transfusion in pediatric cardiac surgery
The rational approach to a bleeding pediatric cardiac surgery patient represents a significant clinical challenge for which the literature often provides limited prospective data. In a study with 75 children, platelet transfusion was most effective for post-CPB bleeding in patients under 8 kg. Continued bleeding was improved with cryoprecipitate but was made worse by plasma in this study [59]. Plasma is often ineffective in children, probably because higher doses are required than the usual 10–15 mL/kg [100,101]. Plasma added to the bypass prime may be beneficial, but the effect seems confined to the smallest patients [102,103]. Fibrinogen concentrates have been proposed as an alternative for cryoprecipitate, but reports of efficacy are limited to the adult cardiac surgery population [104–108].

Objective, laboratory-guided transfusion algorithms have shown significant benefit in adult cardiac surgery [109], but it is difficult to extrapolate these conclusions to children, as adult and pediatric cardiac surgery are qualitatively different [110,111]. Furthermore, not all reports of transfusion algorithms in children have shown positive results [112]. To be clinically useful, laboratory-guided protocols must rely on some reproducible, widely accessible metric. Routine coagulation tests, thromboelastography (TEG), and platelet count can predict postoperative bleeding in children after CPB [113,114], which assists clinicians somewhat in identifying patients at risk. The use of TEG to specifically guide transfusion practice in pediatric cardiac surgery has been reported, with generally favorable results [91,108,115,116]. A recent 2-year retrospective study of an objective transfusion algorithm in pediatric cardiac surgery has shown a significant savings of red cells, cryoprecipitate, and plasma, and a 75%
reduction in mortality following implementation of the algorithm [117].

**Antifibrinolytics in pediatric cardiac surgery**

Antifibrinolytic drugs (aprotinin, aminocaproic acid, and tranexamic acid [TA]) have long been useful adjuvants to cardiac surgery. Reports of their efficacy in children have been less consistent than those in adults. The reader is referred to an excellent review by Eaton [118].

Aprotinin has been used in pediatric cardiac surgery, despite lack of approval by the Food and Drug Administration (FDA) for pediatric use. Endpoints of blood losses and transfusion appear not to be as striking as those for adults, and a wide range of dosing schemes has been reported. Many prospective pediatric trials report hemostatic benefits with aprotinin [119–121], but most show equivocal results [36,92–95,122–124]. One of these studies [124] was terminated early by the FDA due to growing safety concerns in adults [39–42].

Nevertheless, beneficial effects of aprotinin in children extend beyond hemostasis. As mentioned previously, decreased hospital stay, shorter ventilator time, and decreased cost have been associated with aprotinin in children [35–37]. These improvements are probably a result of the anti-inflammatory effects of aprotinin, producing improved organ preservation and suppressed response to extracorporeal circulation.

The lysine analogs (aminocaproic acid and TA) have been the only antifibrinolytics in clinical use since 2006. The lysine analogs probably do have efficacy in children, but less than that of aprotinin [125–127]. As with aprotinin, the efficacy of lysine analogs in children has been inconsistently reported, and differs between subgroups. Pediatric use of aminocaproic acid has been reported, but many of these studies were performed in the 1960s and 1970s, when surgical, anesthetic, and perfusion techniques were quite different from what they are today [128,129]. Williams et al. compared aminocaproic acid with placebo control in an unrandomized study involving 140 children, and demonstrated non-significant decreases in blood losses and transfusion requirements [130]. TA has shown efficacy in children undergoing redo cardiac procedures [96], and in both cyanotic and non-cyanotic patients [131]. An earlier study of pediatric use of TA was only able to demonstrate a reduction in postoperative blood loss in a subset of cyanotic children [132]. In a recent non-blinded trial, both aminocaproic acid and TA were found to be equally beneficial in 150 cyanotic children [133].

**MUF in pediatric cardiac surgery**

Modified ultrafiltration at the conclusion of CPB improves hemostasis, especially for the smallest infants [134,135]. MUF has been used as a method for hemoconcentrating and removing inflammatory factors. Bando et al. compared MUF after CPB with conventional ultrafiltration, and found a 2.5-fold decreased risk of red cell transfusion and six-fold decreased risk of coagulation factor transfusion with MUF [32]. Other investigators have shown similar improvements in post-CPB coagulopathy or transfusion requirements with MUF [136–139]. Additional benefits include improved hemodynamics and cardiac performance [136,137,140,141], decreased ventilatory support [32], and shortened hospital stay [29,139]. However, not all studies report an advantage of MUF over conventional ultrafiltration [134,142]. Also, a recent meta-analysis of eight MUF studies showed improved hematocrit and hemodynamics compared with standard ultrafiltration, but later endpoints were equivocal [143].

**Other methods to minimize transfusion**

Recently, investigators have reported successful use of alterations in perfusion techniques, some of which ablate transfusion altogether, even in very small infants. Minimizing the volume of the pump prime [144–147] and using a miniaturized bypass circuit [147,148] have both shown efficacy for reducing transfusion in small children. Alterations in pump composition, such as a remote pump head, resulted in no transfusion for 122 of 178 infants under 5 kg [149]. Use of washed red cells [150], fresh whole blood [60,146,151], heparin-coated circuits [152], autologous blood prime [153], and anticoagulation management based on heparin concentration rather than ACT [154] have all shown efficacy in the pediatric population.

**Other hemostatic agents**

Recombinant activated factor VII (rFVIIa) has been used with increasing frequency as a rescue hemostatic agent in cardiac surgery since about 2001. Case reports of its use in pediatric cardiac surgery abound [155–159]. The rational use of rFVIIa in pediatric cardiac surgery has recently been reviewed [160]; the author emphasizes the need for randomized trials to clarify efficacy, subgroup analysis of population at risk, and the realistic assessment of thrombotic complications. Desmopressin has minimal hemostatic effects in adult cardiac surgery, and its specific impact in the pediatric population is probably also modest at best, although the available literature is rather dated [161–164]. Chapter 13 contains additional discussion of bleeding and hemostasis.

**Thrombosis in pediatric cardiac surgery**

One major consequence of systemic inflammation and coagulation system activation of CPB is an increased risk of vascular thrombosis. Thrombosis is frustratingly common in children with CHD, as it is associated with significant morbidity [63–67]. In a series of single-ventricle patients, systemic-to-pulmonary shunt occlusion accounted for 9% mortality during a 6-year follow-up [165]. Other authors report a 14% post-discharge mortality in a similar series, 81% of which was sudden and unexpected. Aspirin did not alter risk in this population [166]. In long-term studies, thrombosis has been identified as the first [167] or second [168] most common cause of late mortality in Fontan
patients. Echocardiographic evidence of thrombus exists in as many as a third of asymptomatic children following the Fontan operation [63], with venous thromboembolism and stroke occurring in 19% of these patients [67]. The vascular access necessary for catheterization procedures is associated with a high rate of thrombosis [67], and post-thrombotic syndrome frequently complicates the clinical course [169]. Furthermore, reported incidence rates of thrombosis vary widely between institutions [63,86,170–172].

Risk factors for thrombosis in children with CHD
Thrombosis has some identifiable risk factors. Petaja et al. describe thrombotic events heralded by hypofibrinolysis in a small series of 10 neonates undergoing cardiac operations [73]. In this study, central venous thrombosis was associated with increased PAI-1 levels, and low ATIII and protein C levels. In a review of children with thrombosis and CHD, both acquired and inherited risk factors were found to be significant [169]. Some of these factors included multiple cardiac catheterization procedures, presence of a central venous line, pulmonary stenosis, aortic coarctation, and systemic infection. However, this study identified only 59 subjects with thrombosis and CHD, and an analysis of the interaction between environmental and genetic variables was not performed. Other high-risk patient groups include those with mechanical heart valves, Fontan physiology, endovascular stents, or Blalock–Taussig shunts [64].

The role of FV Leiden (FVL) in this population has been evaluated, but the findings have been difficult to interpret [70,72]. Petaja’s group reported central venous thrombosis in 20 of 1,591 pediatric patients undergoing CPB [72]. Of these, 12 were tested for activated protein C resistance, and two were positive. Ong et al. [70] screened a group of 200 consecutive pediatric cardiac surgery patients for FVL, and prospectively followed them for thrombosis. The prevalence of FVL was 4.5%, not significantly different from the general population, and not significantly associated with thrombotic risk. Protein C sensitivity is associated with the degree of cyanosis in children with CHD, independent of factor VIII levels and FVL [173], suggesting that cyanosis also confers some degree of protection from thrombosis. Box 8.2 summarizes the risk factors for thrombosis.

Current thrombosis management
Because of the significant morbidity associated with thrombosis, accurate risk stratification for the pediatric CHD population would greatly benefit clinical management. However, current clinical tests do not quantify hypercoagulability. Instead, hypercoagulability can only be determined through non-standard coagulation tests, or using surrogate markers such as previous thrombosis or disseminated intravascular coagulation. In addition, because the extent and duration of hypercoagulability associated with specific congenital heart lesions have not been reported, both the duration and intensity of anticoagulant treatment for hypercoagulable congenital heart patients are unknown. Routine screening of all congenital heart patients for pre-existing hypercoagulable conditions is rarely performed, as it is costly and time-consuming, with unclear clinical utility.

Because a rapid and cost-effective laboratory test to quantify hypercoagulability does not yet exist, congenital heart patients are treated with an anticoagulant regimen unique to the institution [63,86,170–172]. This approach potentially places these children at serious risk of either under- or over-treatment [171,174,175]. Aspirin is currently used in 54%, and warfarin in 43%, of Fontan patients in a recent review [176]. Yet, aspirin resistance is common in children with CHD [177], although most centers do not make use of sensitivity data prior to prescribing aspirin in this population [177]. Clopidogrel is currently in use at some pediatric heart centers [178–181], but individual patient response varies widely [179] and dose–response testing is cumbersome and expensive.

Prospective trials of antithrombotic therapy in children with CHD do not offer much guidance, as they often suffer from small sample size or equivocal results. A randomized multicenter trial of clopidogrel vs. a placebo in children with systemic pulmonary shunts found no benefit of clopidogrel when added to conventional therapy [182]. A multicenter study in Fontan patients randomized 111 children to receive either aspirin or heparin with warfarin after the operation, and followed the subjects for 2 years, surveying for thrombosis by echocardiography [183]. There was no significant difference in thrombosis risk between the two groups. Importantly, thrombosis occurred at a high rate (23% of subjects), which underscores the ineffectiveness of current management strategies and the inability to identify high-risk subgroups. A network for future prospective trials in the Fontan population is currently being formed [184]. Despite many current management recommendations, thrombosis still occurs [67,175,185], and there is no intermediate laboratory phenotype to help refine risk assessment or guide therapy [186]. Consensus recommendations for antithrombotic therapy in children with CHD are included in the latest guidelines from the American College of Chest physicians [187], but the strength of the recommendations and quality of the supporting evidence are admittedly often weak.

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**Box 8.2: Risk factors for thrombosis in children with congenital heart disease**

- Presence of a central venous line
- Multiple intravascular interventions
- Pulmonary or aortic stenotic lesions
- Cyanosis
- Polycythemia
- Cavopulmonary anastomosis
KEY POINTS: EFFECTS OF CONGENITAL HEART SURGERY ON COAGULATION, HEMOSTASIS, AND THROMBOSIS

• Coagulation in cyanotic CHD is altered by cyanosis and surgery overlaid upon normal developmental coagulation
• Bypass induces activation of the coagulation and fibrinolytic systems, placing cyanotic, thrombocytopenic infants at greatest risk for postoperative hemorrhage
• Lysine analogs have efficacy in bypass, especially cyanotic or resternotomy patients
• Aprotinin improves hemostasis and hemodynamics, and reduces inflammatory response, and ICU stay
• MUF improves hemostasis and other clinical outcomes
• Thrombosis is a source of significant morbidity, and is incompletely understood.
• Although treatment guidelines have been issued, primary prevention of thrombosis in children with CHD suffers from lack of strong supporting data.

Pulmonary effects of congenital heart surgery

Neonatal and pediatric pulmonary physiology: a compromised state

All physiologic systems carry an inherent amount of reserve, which is the capacity to increase their function to maintain homeostasis in the setting of a physiologic compromise. The pulmonary system is indeed able to compensate for injury by increasing ventilation and redistributing pulmonary flow. However, there are numerous features of the pediatric pulmonary system that place infants and children at increased risk of pulmonary failure in the setting of systemic injury. These are summarized in Box 8.3.

Metabolic compromise

The demands placed on the respiratory system of children are greater at baseline than those of adults, because of the increased metabolic rate of childhood [188]. Infants and young children, being in the active phases of growth and development, consume two to three times as much oxygen on a per kg basis [189], and generate correspondingly more carbon dioxide than do older children or adults. Furthermore, hypoxic and hypercapnic drive of ventilation is attenuated in infants compared with older children or adults [190,191]. Compromise of ventilation will therefore lead to respiratory failure sooner, and failure will accelerate faster in children, especially infants.

Mechanical compromise

Air movement in and out of the lungs is driven by muscular actions on the bony structures of the chest. The diaphragm is the principal muscle of ventilation, but intercostals, scalenes, sternocleidomastoid, and even pectorals can be recruited in sequence as respiratory function demands. In children, the horizontal positioning of the ribs, and the increased compliance of non-ossified bone, renders the intercostals and other accessory muscles at a distinct mechanical disadvantage [191,192]. Hence, the diaphragm must assume a greater share of respiratory work, and recruitment of accessory muscles offers less of an advantage.

The diaphragm of the infant, however, is less able to sustain increased aerobic work than that of the older child. Small children are also less able to increase their tidal volumes and therefore must increase minute ventilation by increases in respiratory rate. The diaphragm and intercostal muscles of young infants have fewer of the type I, slow-twitch fibers than do the corresponding muscles of older children or adults [193]. These fibers are uniquely capable of higher oxidative capacity and offer a degree of insurance against fatigue when ventilatory demands are increased.

Ventilatory compromise

The resting ventilation of infants and young children differs markedly from that of older children in its classic spirometry. Because total lung capacity (TLC) is an effort-driven parameter, the TLC of an adult on a weight basis is much greater than that of a small child. Functional residual capacity (FRC) is defined as the lung capacity at which the elastic recoil forces of the lung and the passive recoil of the chest wall are equal, and represents the volume in the lungs at the time of end expiration during quiet breathing. For infants and small children, FRC is significantly reduced, so a hypoventilating or apneic infant sequesters a disproportionately smaller reserve of intrapulmonary oxygen than an older child, leading to a more rapid development of hypoxemia [194,195].
The closing volume of an infant’s smaller airways is within the range of the infant’s normal tidal volume [191,194,196]. This means that during normal ventilation, some of the smaller airways close, resulting in air trapping. A specific lung volume is therefore not in communication with extrapulmonary air, possibly leading to atelectasis, ventilation–perfusion mismatching, and hypoxemia. Awake infants can re-establish their lung volumes by crying, deep vital capacity breathing, sighing and movement, all of which are diminished or ablated by iatrogenic interventions such as anesthesia and sedation.

While small airway resistance contributes about 20% to the total airway resistance of the adult airway, these smaller airways contribute about half of the total airway resistance in infants [197–199]. Therefore, inflammatory injury to the lung, which results in small airway edema and lumen narrowing, makes a greater contribution to obstructive airway disease in smaller children. In the cardiac setting, this is highly relevant, as the inflammation associated with CPB, and edema resulting from volume overload or increased pulmonary venous pressures are common.

The lungs of children have not finished growing. Although the major parts of the bronchial tree are formed during gestation, expansion of the alveolar population continues into the eighth year of life. Pulmonary vessel growth follows the development of alveoli. Smooth muscle development in pulmonary arteries of normal lungs is complete in adolescence.

Compromise of neonatal oxygen delivery
Very young infants can experience transpulmonary shunting, hypoxemia, and impaired oxygen delivery for other reasons. A newborn infant’s lungs occasionally retain residual lung fluid, which contributes to transient tachypnea of the newborn [200]. This is often, but not always, self-limiting. Atelectasis in the first few days of life in term neonates or in preterm infants due to surfactant deficiency can also contribute to shunting [201]. Fetal hemoglobin has a significantly attenuated shift of its oxygen affinity in the presence of increased 2,3-diphosphoglycerate [202], which can compromise neonatal oxygen delivery in the setting of anemia or tissue hypoxia states.

Compromise arising from CHD
Congenital heart disease further imposes another set of unique compromises to the pediatric pulmonary system. Pulmonary hypertension, most often arising from pre-existing pulmonary vascular disease (PVD), is a frequent and often predictable sequela of pulmonary overcirculation, and portends significant perioperative morbidity [203–205]. PVD develops as increased pulmonary flow produces a recognized histologic pattern of pulmonary vascular remodeling. PVD increases in severity with both the duration and magnitude of excessive pulmonary blood flow. In normal neonates, pulmonary vascular endothelium and vascular smooth muscle continue to develop into their mature phenotypes after birth and throughout the first years of childhood. When pulmonary flow is excessive, a different developmental trajectory is followed, with histologic evidence of medial hypertrophy, intimal hyperplasia, and decreased numbers of interacinar arteries being evident within months [206]. A histologic grading system, known as the Heath–Edwards classification, is used to assign a severity score to these changes (on a scale of 1–6). The Heath–Edwards grade predicts reversibility of PVD changes upon correction of excessive pulmonary flow. Pulmonary resistance is increased in PVD, and pulmonary vessels in PVD have increased sensitivity to vasoconstrictive stimuli of hypoxemia, hypercarbia, and acidosis, placing the patient with PVD at significant risk for perioperative cardiac failure [207]. Indeed, pulmonary hypertension, regardless of cause, continues to be a major risk factor for heart failure and other cardiac complications in patients with CHD. However, as hemodynamic data from the catheterization laboratory correlates with histologic grade [208], and lung biopsy carries significant risk, biopsy is not routinely used to assess prognosis in univentricular heart surgery [206,208–211].

Cardiac performance significantly impacts pulmonary function. Increased pulmonary venous pressure, whether from arrhythmia, valve dysfunction, systolic dysfunction, or obstructive lesions, results in increased lung water and interstitial edema [212]. In the cardiac surgical setting, this can have disastrous effects on pulmonary compliance and gas exchange, elevating the work of breathing for what is often an already compromised patient. This is discussed in greater detail below.

Pediatric cardiac surgery patients often have impaired nutritional status, an often under-appreciated aspect of clinical care [213]. Approximately one in four children with CHD meets the criteria for failure to thrive within the first year of life, and half of those with single-ventricle physiology require supplemental tube feeding [214]. The consequences of delayed growth and suboptimal nutrition for the cardiorespiratory system are not simply a matter of size [215]. Respiratory muscle drive and cardiac performance are measurably impaired in malnutrition [216–219]. Both humoral and cell-mediated immune suppression render the malnourished child susceptible to perioperative infection [219–221]. Growth failure in the congenital heart surgery population has been associated with longer hospital length of stay, increased risk for infection, worse neurodevelopmental outcome, and mortality [214].

Finally, children with congenital heart malformations often have other associated anomalies of the head, neck, mandible, teeth, and upper airway. CHARGE, VACTERL, and Down syndromes frequently have associated malformations which can make it difficult to secure the airway by the standard means of direct laryngoscopy [222–226]. When these difficulties are appreciated, alternative approaches of airway management can be considered.
If such difficulties are not appreciated, these associated anomalies can lead to prolonged apnea, failure to ventilate, and possibly airway disasters. When extubation is planned, a greater degree of ventilatory performance is probably prudent to prevent the urgent need for reintubation under suboptimal circumstances.

It is therefore no surprise that children with CHD face a perioperative course fraught with potential pulmonary complications. Indeed, pulmonary complications represent significant sources of perioperative morbidity and mortality [227–230], increasing in severity and frequency with the decreasing age of the child. In a recent Polish study of nearly 700 children with CHD, preoperative respiratory insufficiency predicted the longest postoperative length of ICU stay [231].

**Effects of CPB on pulmonary physiology in children**

**CPB and PVR**

The obligatory mechanical support of the circulation during repair of congenital heart lesions is by no means a benign intervention. The coagulation system is severely attenuated while the entire blood volume of the patient is circulated in an elaborate system of plastic polymers and uncoated steel for an unspecified duration, during which time the entire patient is intentionally cooled to non-physiologic temperatures. During much of this time, there is often no coronary flow, pulmonary flow is almost completely arrested, and perfusion to the remaining vital organs loses the pulsatile waveform under which these organs have thrived and evolved. Blood in contact with TF-bearing surfaces is often returned directly to circulation, and hemolysis is generated from suctioning and blood–air contact. Reperfusion and rewarming release the heralded cascade of ischemia–reperfusion responses, and post-bypass transfusion brings a flood of transplanted cells and proteins from a genetically distinct host. The lungs, now receiving 100% of the cardiac output (in a two-ventricle repair), bearing a massive area for gas exchange in a delicate capillary bed, and having an exquisitely sensitive arterial tree, respond profoundly to these perturbations, both local and remote.

Increased PVR, therefore, frequently complicates the postoperative care of pediatric cardiac surgery patients [232–234], and represents a major risk factor for morbidity. In various pediatric cardiac populations, increased PVR is associated with prolonged duration of ICU stay [231,235,236], prolonged duration of mechanical ventilation [236,237], and increased postoperative mortality [232,238]. It is a gross simplification to attribute the important postoperative increase in PVR to a single vasoactive mediator or process. Direct causes of increased PVR in the postoperative patient are quite numerous and include increased reactivity of the pulmonary vasculature, duration of CPB, hypothermia, acidosis, endothelial dysfunction, and pre-existing pulmonary vascular disease [232].

The endothelium is a pivotal tissue in the pathophysiology of elevated PVR following cardiac surgery. Through its secretion of vasorelaxant prostanoids and nitric oxide, the endothelium guards against unopposed vasoconstriction mediated by catecholamines, angiotensin, and endothelin [239]. This relaxant function is acutely disrupted by CPB [240–243]. Although the cellular and subcellular mechanisms responsible for CPB-induced endothelial dysfunction have not been completely characterized, pulmonary ischemia–reperfusion injury is thought to be crucial in its etiology [243,244], despite early conjectures that the bronchial circulation provided adequate maintenance of pulmonary perfusion during CPB. Continuous perfusion of the lungs during CPB has been shown to improve oxygenation and decrease duration of postoperative mechanical ventilation in children [243,245]. In fact, the perfusate need not even be blood; in a small prospective trial, lung perfusion with blood-free organ preservation solution during CPB resulted in improved oxygenation and decreased inflammatory response [246]. Laboratory studies have recently provided evidence for calpain and NF-κB as molecular mediators responsible for this ischemia-related increase in PVR [247,248]. Box 8.4 summarizes the effects of cardiac surgery on lung physiology.

**Box 8.4: Effects of cardiac surgery on lung physiology in children**

- Ischemia–reperfusion injury
  - Impaired endothelial-dependent relaxation
  - Increased vasoreactivity of pulmonary vasculature
  - Increased lung water
  - Impaired gas exchange
  - Reduced lung compliance
- Decreased surfactant production and quality
- Atelectasis of lung segments or lobes
- Transpulmonary shunting
- Loss of lung volumes from deflation during cardiopulmonary bypass or presence of devices

**Management of post-CPB pulmonary hypertension**

Because CPB-induced increase in PVR is the result of a complex interplay of inflammation, reperfusion, and endothelial dysfunction, clinicians have successfully intervened with therapies directed toward a multitude of cellular and physiologic pathways. General measures include optimization of hematocrit, pH, ionized calcium and other electrolytes, temperature, adequate ventilation, high-dose narcotic, neuromuscular blockade, and treatment of arrhythmias. Pulmonary vasodilators (nitric oxide and its donors, phosphodiesterase inhibitors, and prostaglandin analogs) and inotropic support constitute the mainstay of specific therapy, as discussed below [249]. Recently, additional adjunctive treatments involving anti-inflammatory agents [250], antioxidants [251], and protease inhibitors [248] have shown some usefulness. In practice, pulmonary hypertension and right ventricular
failure often involve multimodal management with a variety of agents and therapies [252]. Soon after the discovery of nitric oxide as the fundamental endothelial-derived vasodilator, inhaled nitric oxide (iNO) was employed as an agent to treat pulmonary hypertension [253,254]. Nitric oxide is a small molecule that diffuses rapidly across membranes and has a biological half-life of only a few seconds owing to its rapid binding and inactivation by hemoglobin. It binds reversibly to and activates soluble guanylate cyclase, which catalyzes the conversion of guanosine 5’-triphosphate (GTP) to cyclic guanosine monophosphate (cGMP). This subsequent messenger activates cGMP-dependent protein kinase, which phosphorylates various proteins and causes vasodilation in multiple vascular beds [255]. Because the duration of action of nitric oxide is so short, iNO has the advantage of selectively dilating pulmonary arteries.

Clinical use of iNO has expanded dramatically since its discovery, because of its relatively low toxicity at doses less than 20 ppm, selectivity of the pulmonary vascular bed, efficacy in numerous settings, and ease of administration in ventilated patients [256–258]. In pediatric cardiac surgery, iNO has shown efficacy in reducing pulmonary pressures and improving oxygenation and right ventricular function [259–261]. Patients most likely to respond to iNO appear to be those with elevated preoperative PVR, although some with the highest PVR may be unresponsive [262, 263]. However, despite the efficacy of iNO in improving pulmonary resistance and hemodynamics in the acute postoperative setting, there are limited data from prospective, randomized trials [264]. A recent Cochrane review was inconclusive, owing to heterogeneity of populations, inherent publication bias, and lack of quality data [265]. Because the cost of administration of iNO is high (about $3,000 US per day) [266], large-scale, multicenter studies are needed to better define the congenital heart population most likely to experience long-term benefit.

Toxicity of iNO is very low at clinically relevant concentrations. Methemoglobinemia is a potential problem if high doses (>80 ppm) are administered for an extended time, or for patients with genetic deficiency of methemoglobin reductase [267]. Peroxynitrite results from the reaction of nitric oxide with superoxide, and is a potent oxidant and pulmonary irritant. In high concentrations, peroxynitrite can damage DNA, induce apoptosis, and impair the vasorelaxant function of endothelium [267]. Inhaled nitric oxide also increases endothelin-1 (ET-1) secretion, which may account for some of the rebound pulmonary hypertension observed when iNO is discontinued [268].

Nitric oxide donors and precursors have been employed in the treatment of increased PVR in the postoperative setting. Nitric oxide is a product of arginine, an amino acid in the urea cycle. Since low levels of urea cycle intermediates have been observed in CHD patients following CPB [269], investigators have successfully prevented postoperative pulmonary hypertension in children by supplementation with both oral [270] and intravenous citrulline [271], lending further evidence to the pivotal role of the pulmonary endothelium. Nitroglycerin is a potent nitric oxide donor with a very short half-life, and has been useful in pediatric cardiac surgery [272]. However, nitroglycerin is a non-specific vasodilator and preferentially dilates the venous circulation, potentially leading to decreased preload and decreased cardiac output.

Inhaled epoprostenol (prostacyclin) is a prostaglandin analog with non-specific vasodilating properties. It acts via specific membrane receptors to increase intracellular cAMP and therefore activate cAMP-dependent protein kinases. Long-term management of pulmonary hypertension, related or unrelated to CHD, often involves intravenous infusion of epoprostenol [258,273]. Prostacyclin has shown efficacy for both adults and children with pulmonary hypertension related to CHD [274]. Inhaled prostacyclin shares the advantage of iNO, in that both treatments are very selective for the pulmonary vasculature and have little, if any, effect on systemic vascular resistance. In the post-transplant cardiac surgery population, a large randomized trial found no difference in efficacy between iNO and prostacyclin [275]. In an uncontrolled case series of post-CPB pediatric patients, inhaled prostacyclin was effective at decreasing pulmonary pressure, but one-third of the subjects required norepinephrine as a systemic vasoconstrictor agent, indicating that this agent is somewhat less selective for the pulmonary vasculature than iNO [276].

Phosphodiesterase inhibitors (PDEIs) represent another pharmacological approach to increased PVR. These agents increase the intracellular levels of cyclic nucleotides (cAMP and cGMP) by inhibiting enzymes responsible for their breakdown. PDEIs selective for phosphodiesterase 5 inhibit breakdown of cGMP and are therefore vasodilatory, with sildenafil being the agent in most frequent clinical use. Sildenafil has been useful for managing both idiopathic pulmonary hypertension and pulmonary hypertension associated with CHD in children [277]. In laboratory models of pulmonary hypertension, PDEIs have shown efficacy both alone and in combination with other agents [278–280]. Because of its favorable safety profile, its use has been expanding in recent years, especially in the pediatric population [281–285]. However, the quality of the evidence for many of these studies is suboptimal, relying on retrospective associations and prospective studies with small sample size or in limited populations, making it difficult to extrapolate their findings to other populations or practices.

Endothelin-1 is a vasoconstrictive peptide released from endothelium. In the pulmonary circulation, ET-1 binds to specific ET(A) receptors on smooth muscle and initiates protein kinase C activation and increased intracellular calcium levels, producing vasoconstriction. In recent years, specific ET(A) receptor antagonists have been effective for treatment of pulmonary hypertension, specifically in the post-CPB setting [286,287]. As in the case for PDEIs, ET(A) receptor antagonists were first used in outpatients for the management of idiopathic pulmonary hypertension, and their clinical application expanded from there into the cardiac surgery, transplant, and ICU settings [273,288–292]. Also, as in the case for
Transfusion-related acute lung injury (TRALI) is most likely caused by donor antibodies directed against recipient leukocytes [303], plasma is often the cause, although identity of the offending blood unit is not part of the case definition. In pediatric cardiac surgery, transfusion of blood products is significantly associated with postoperative morbidity, including pulmonary complications [54], but it is unclear what role immunologically identified TRALI may have in this association, and to what extent blood transfusion is simply a marker for case complexity. TRALI appears to be less common in children than in adults, although part of this observation may be a result of under-reporting or under-recognition [304].

**Techniques to improve respiratory function**

Multiple strategies have been proposed for improving gas exchange and lung compliance [305]; these largely focus on controlling two processes: reduction of lung water and prevention of atelectasis [306].

As pulmonary edema is a result of inflammation, reperfusion, and oxidative injury, efforts to control or reduce pulmonary edema have focused on these pathophysiologic processes. Although activated neutrophils directly disrupt the pulmonary capillary barrier, leukocyte depletion of circulating blood has shown modest or inconsistent results, and depends significantly on the population being studied [307–309]. Leukocyte depletion has been reported for the CPB pump prime [310], residual pump blood [311,312], or continuous leukofiltering during CPB [313–317]. Interestingly, improved respiratory function has been achieved in this setting with the use of neutrophil elastase inhibitors [318]. Many of these studies report data from experimental animal models or adult patients, so extrapolation to children may not necessarily be valid, although one author has identified children as a population most likely to benefit [309].

Pulmonary perfusion during CPB avoids reperfusion injury, and therefore lung edema, by omitting a period of lung ischemia. Apparently bronchial circulation is insufficient alone to meet metabolic demands of the lung for a sustained period of time. Lung water and markers of inflammation can be significantly attenuated by pulmonary perfusion during CPB, either with blood or with a protectant solution [243,245,246,319,320]. Improved oxygenation is also achieved by maintaining lung perfusion during CPB.

Pulmonary injury and dysfunction resulting from TRALI can be prevented by minimizing transfusion, especially of plasma and cryoprecipitate. Efforts to optimize blood transfusion are discussed earlier in this chapter. Supportive care is the mainstay of treatment, consisting of oxygen supplementation, non-invasive or invasive ventilation, positive end-expiratory pressure (PEEP), and diuresis [321]. Notification of the blood bank is prudent when TRALI is suspected, as donor identification may prevent future cases [322].

Modified ultrafiltration, mentioned previously for its benefits in attenuating pulmonary vasoreactivity following pediatric CPB, has shown benefit for the removal of lung water, resulting in increased lung compliance and
improved gas exchange [323–328], with the effect being most notable within the first 6 hours postoperatively. MUF also decreases the duration of mechanical ventilation following congenital heart surgery [326,329,330], with the youngest infants most likely to benefit [326].

Atelectasis in small infants is often due to deficient or dysfunctional surfactant. Surfactant is a physiologic necessity for maintaining airway and alveolar patency during ventilation, and CPB has deleterious effects on measures of surfactant activity [301,302,331,332]. A recent retrospective study of exogenous surfactant for infants with respiratory distress syndrome after cardiac surgery reported an improvement in oxygenation index, and shorter duration of mechanical ventilation and hospital stay when compared with historical controls [333]. Other authors have reported benefits of pulmonary surfactant supplementation in children with CHD during extracorporeal membrane oxygenation [334,335] or in respiratory distress outside the perioperative period [336].

The routine practice of suspending ventilation during CPB results in near-total atelectasis by the end of CPB. Recruitment of collapsed alveoli and maintenance of ventilation are necessary for separation from CPB. While a sustained inflation (recruitment maneuver) alone is probably ineffective for maintaining open alveoli, it can effectively prevent atelectasis well into the postoperative period when followed by maintenance of PEEP [337,338]. But these findings are based on adult data and have not been duplicated in children. However, a recent randomized study of dornase alpha (a mucolytic agent) after pediatric CPB reported significantly improved radiographic atelectasis scores and oxygenation as compared with controls receiving chest physiotherapy [339].

**KEY POINTS: PULMONARY EFFECTS OF CONGENITAL HEART SURGERY**

- Ventilation in infants is physiologically compromised, compared with older children.
- Pulmonary vascular disease results from increased pulmonary blood flow, causing increased vascular resistance, increased sensitivity to vasoconstrictor stimuli, and histologic changes.
- Multiple factors increase PVR following CPB: ischemia–reperfusion injury, endothelial dysfunction, and pre-existing pulmonary vascular disease.
- Management of post-CPB PVR is with vasodilators: inhaled nitric oxide, prostanoids, and phosphodiesterase inhibitors.
- The direct effects of pulmonary capillary leak are decreased pulmonary compliance and decreased gas exchange.
- Avoidance of ischemia–reperfusion, use of MUF, and recruitment of atelectatic lung segments decrease clinical impact of pulmonary capillary leak.

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**Renal effects of congenital heart surgery**

**Introduction, incidence, and definition of the problem**

Renal injury is a well-known complication of the surgical management of CHD. Depending on the outcome definition, and the population under study, acute kidney injury (AKI) affects up to 64% of children requiring CPB [340–342]. The incidence is difficult to quantify accurately due to the range of definitions of acute renal failure (ARF) and significant institutional variability in the institution of renal replacement therapy [343,344]. Renal injury following CPB is thought to be the result of hypotension, systemic inflammatory response, and perioperative use of nephrotoxic medications [340,341,345].

Several studies have identified perioperative factors that increase risk to the kidney. Younger age, smaller size, duration of CPB and aortic cross-clamp, intraoperative transfusion, early postoperative hypotension, 24-hour postoperative lactate levels, duration of mechanical ventilation, and vasopressor use have all been associated with renal injury [340,342,344–348]. Genetic factors have also been identified [349]. Renal injury co-associates with many risk factors for postoperative LCOS, so the association of renal injury with inotropic support may represent an epiphenomenon. The PRIMACOR study, in fact, found no independent association of reduced postoperative creatinine clearance with the use of milrinone [350]. In a retrospective study examining the risk of ARF after cardiac surgery preceded by cardiac catheterization, young age, amount of iodinated contrast received, and presence of LCOS were identified as risk factors. Age less than 2 years was associated with a 20-fold increase in the risk of perioperative AKI in children who underwent preoperative cardiac catheterization [351].

Younger children are particularly prone to renal injury, as the kidney of an infant functions less effectively until approximately 2–3 years of age [352]. Infants have decreased glomerular filtration rate (GFR) due to increased renal vascular resistance in the setting of low mean arterial pressure. When decreased GFR is considered in the setting of immature tubular cell function, tubular reabsorption is substantially impaired when compared with adult patients. Given that many challenging cardiac operations occur in the newborn period, it is little surprise that an increased incidence of renal dysfunction is seen in the youngest patients, independent of immature renal function.

One operational cause of our inability to understand or predict the occurrence of AKI following congenital heart surgery has been the lack of a consistent definition of AKI across studies. In 2001 the Acute Dialysis Quality Initiative Group proposed the adult RIFLE (risk, injury, failure, loss and end-stage renal disease), which aimed to standardize the definition of AKI and stratify kidney injury based on degree of elevation of serum creatinine, decrease in estimated GFR, or prolonged oliguria. The pediatric modification of the RIFLE score (pRIFLE) detects
Table 8.2 Pediatric RIFLE (risk, injury, failure, loss and end-stage renal disease) score

<table>
<thead>
<tr>
<th>pRIFLE criteria</th>
<th>Estimated creatinine clearance</th>
<th>Serum creatinine (SCr)</th>
<th>Urine output</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Early</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R (risk)</td>
<td>25% decrease</td>
<td>1.5 x baseline</td>
<td>&lt;0.5 mL/kg/hour x 8 hours</td>
</tr>
<tr>
<td>I (injury)</td>
<td>50% decrease</td>
<td>2 x baseline</td>
<td>&lt;0.5 mL/kg/hour x 12 hours</td>
</tr>
<tr>
<td>F (failure)</td>
<td>75% decrease</td>
<td>3 x baseline</td>
<td>&lt;0.5 mL/kg/hour x 24 hours or anuria</td>
</tr>
<tr>
<td><strong>Late</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L (loss)</td>
<td>Renal failure &gt; 4 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E (end stage)</td>
<td>Renal failure &gt; 3 months</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 8.7 Serum cystatin C in children aged 3 months (mo) to 16 years (y). The box plot extends from the 25th percentile to the 75th percentile, with the horizontal line at the median, and the whiskers show the central 95% of the data for the Alfresa assay. (Source: Yata et al. [357]. Reproduced with permission of Springer.)

acute renal injury in critically ill children [353,354], and is a predictor of length of stay and mortality, independent of the Pediatric Risk of Mortality (PRISM) score [353]. Pediatric RIFLE scoring stratifies renal dysfunction based on reduction in estimated creatinine clearance, elevation in serum creatinine above baseline or reductions in urine output (Table 8.2). The Acute Kidney Injury Network has devised a similar score, the AKIN score, which appears to correlate well with pRIFLE [341,353]. Late renal failure (pRIFLE categories L and E), however, remains difficult to define in the postoperative congenital cardiac population, due to wide variation in postoperative use of peritoneal dialysis [355]. Small increases in serum creatinine in the early postoperative period predict kidney injury using the pRIFLE criteria, and more severe renal injury predicts worse clinical outcomes. Importantly, while progress has been made in the staging and characterization of renal dysfunction, many studies also vary in their postoperative observation window, accounting for some variability in reported incidence.

**Emerging biomarkers of renal dysfunction**

Serum creatinine is most commonly used to estimate GFR, the volume of filtrate entering the renal tubules at the glomerulus per unit of time. Estimates of GFR using serum creatinine measurements may be insensitive indicators; serum creatinine often does not rise until GFR falls below 80 mL/min/1.73 m². Because creatinine is also secreted by the proximal tubule, GFR may be reduced by up to 50% before elevations in serum creatinine are observed [356]. There is substantial interest in other potential indicators of renal dysfunction, which are more sensitive to declining GFR, and reflect renal function in real time. Cystatin C is a cysteine protease inhibitor produced by nucleated cells throughout the body at a constant rate. It is filtered at the glomerulus and not secreted by tubules. Normal levels of cystatin C are somewhat higher in neonates and small infants [357] (Figure 8.7). Serum cystatin C levels show stronger correlation with measured GFR than do serum creatinine levels in young children and adolescents [358]. Although data on its use in congenital heart surgery are just beginning to be described, cystatin C is emerging as a highly sensitive indicator of renal dysfunction in children following cardiac surgery, and serum elevation of cystatin C occurs within hours of injury to the kidney [359,360] (Figure 8.8). Cystatin C concentrations correlate with

Figure 8.8 Serum cystatin C levels in patients with and without acute kidney injury (AKI) over the study period. Cystatin (cys) C levels displayed as least-square means (± SE). *P*-values obtained using differences of least-square means after Tukey–Kramer adjustment. P-value < 0.05. (Source: Hassinger et al. [360]. Reproduced with permission of Lippincott, Williams & Wilkins.)
severity of AKI (defined by pRIFLE criteria) beginning 2 hours after CPB. Interestingly, half of the patients included in this study were less than 2 years of age. The first postoperative cystatin C levels and the postoperative cystatin C changes from baseline value were independently associated with duration of mechanical ventilation in this study, whereas serum creatinine levels were not [359]. The clinical utility of cystatin C remains to be determined, specifically in newborns and young infants.

**Association of renal injury with clinical outcomes**

In adult cardiac surgery, even mild renal dysfunction is associated with greater length of hospital stay, cost, and mortality. It is unclear to what degree these associations also exist for children. Many authors have studied this question using retrospective data, and have reported associations between poor clinical outcomes and mild renal dysfunction. Some studies, however, are small or do not control for sufficient covariates.

Although mild AKI may or may not portend significant clinical consequences for children, it is clear that the more severe forms of perioperative AKI are significant harbingers of poor outcome. Toth et al., using propensity-matching, observed AKI in 32% of patients, with 11.5% meeting criteria for risk, 1.7% for injury, and 18.7% for failure by pRIFLE [361]. They further reported an association between AKI, increased length of ICU stay and mechanical ventilation, but not in-hospital mortality in their 1510-patient cohort. Morgan et al. studied the neonatal population for a follow-up of 2 years, and found AKI in 64% of subjects, as defined by AKIN criteria [342]. AKI was associated with duration of mechanical ventilation, length of ICU stay and length of hospital stay after accounting for covariates by regression [342]. They observed an increase in 2-year mortality in patients with AKIN stage 2 or higher [342,362]. In a retrospective cohort of 409 children undergoing congenital cardiac surgery, early AKI by pRIFLE criteria was observed in 20% of subjects, and was associated with length of ICU stay, duration of mechanical ventilation, and mortality [363]. In another retrospective cohort of 693 postoperative cardiac patients, investigators observed a 15% incidence of AKI (11% mild, 3% moderate, 1% severe), by AKIN criteria. These investigators observed that only moderate and severe AKI were associated with prolonged postoperative recovery [347].

**Renal failure and renal replacement therapy following cardiac surgery in children**

The use of renal replacement therapy for postoperative renal failure is difficult to determine given the variability in practice patterns. In patients with severe hemodynamic instability, continuous veno-venous hemofiltration (CVVH) may provide the optimal means of renal replacement therapy. Most patients, however, will tolerate the initiation of peritoneal dialysis (PD), as a means of augmenting the function of failing kidneys, as a method of avoiding volume overload, or as a means of modulating the inflammatory response seen post-CPB in these children. There is some suggestion that early initiation of PD in this population might improve survival following cardiac surgery [364].

**Peritoneal dialysis**

Peritoneal dialysis is frequently used in postoperative management of patients following cardiac surgery. Although initial application in this population was intended for management of postoperative renal failure, its indications have expanded to include fluid overload, optimization of cardiac loading conditions, decompression of the abdominal cavity, and mitigation of the inflammatory sequelae of CPB. Peritoneal drainage catheters (PDCs) can be used either as a passive drain in the abdominal cavity or as a means of initiating peritoneal dialysis for active fluid and electrolyte management. A recent analysis of data from 2006 and 2009 in the Kids’ Inpatient Database in this population found that young age, higher Risk Adjustment for Congenital Heart Surgery (RACHS-1) score, acute renal failure, CPB, non-elective admission and hospital region in the south or west were associated with increased rates of PD catheter placement [355]. There is widespread variability in the indications and frequency for PD in pediatric cardiac surgical patients across institutions, although those patients undergoing PDC placement represent a relatively high-risk subset within the postoperative population [355].

Peritoneal dialysis carries some risk. In a review of 1,128 patients undergoing congenital cardiac surgery who underwent PDC placement, 130 developed complications. Most events were minor and included leakage and mechanical dysfunction, 6.2% developed severe complications (hydrothorax, hemoperitoneum, bowel perforation, and peritonitis). However, mortality in patients with PD complications was not significantly different than those without PD complications [365].

**Peritoneal dialysis in the management of postoperative fluid overload**

Fluid overload is often seen in young patients following CPB. As outlined extensively in this chapter, capillary leak associated with CPB, transfusion, administration of crystalloid, myocardial dysfunction, and activation of the renin–angiotensin–aldosterone system all contribute to postoperative fluid overload. Reduced GFR and medullary concentrating ability in young children also predispose to fluid overload. Fluid overload can delay sternal closure, prolong duration of mechanical ventilation, and limit the ability of the gastrointestinal tract to process enteral nutrition properly. Fluid overload as measured by daily
weight is associated with worse clinical outcome among infants undergoing cardiac surgery [366].

The use of PDCs allows for the safe and effective removal of fluid during the postoperative period. It improves early postoperative hemodynamics and improves ICU outcomes [367–369]. In two different observational studies of children undergoing congenital cardiac surgery, early peritoneal dialysis was associated with a significantly negative fluid balance [369,370].

**Peritoneal dialysis for the mitigation of the systemic inflammatory response**

Peritoneal dialysis can mitigate the inflammatory response to CPB. In congenital heart surgery, serum IL-6 levels have been associated with AKI and duration of mechanical ventilation [371], and PD removes proinflammatory cytokines IL-6 and IL-8 [372]. In an observational study comparing passive peritoneal drainage and diuresis with PD, the latter was associated with earlier sternal closure (24 vs. 63 hours), lower mean inotropic scores, shorter duration of mechanical ventilation (71 vs. 125 hours), and greater net negative fluid balance [373].

**Continuous veno-venous hemofiltration**

Hemodialysis allows for volume and solute management using ultrafiltration and diffusion across a semi-permeable membrane. When done intermittently, it results in rapid shifts of solute and solvent, and a large extracorporeal volume burden, which makes it an unpopular choice in the postoperative population. CVVH is thought to be a better-tolerated means of volume management used in postoperative cardiac surgery patients. Anticoagulation is necessary to maintain patency of CVVH systems, and complications can arise related to vascular access for CVVH. In the event that more aggressive solute clearance is required, continuous veno-venous hemodialysis may be required, in which case dialysis fluid is introduced into the hemofiltration cartridge, which increases electrolyte clearance. Hypokalemia is frequently seen during this procedure and potassium may be added to the dialysis solution to avoid this complication.

**KEY POINTS: RENAL EFFECTS OF CONGENITAL HEART SURGERY**

- Impaired renal function is common after bypass and is most frequent and severe in infants undergoing complex operations.
- Studies of perioperative renal injury in children are contradictory because of differences in endpoint definition and monitoring windows.
- Perioperative renal injury is associated with poor clinical outcomes – duration of mechanical ventilation, length of ICU and hospital stay, and mortality – with worse injury associated with worse outcome.
- Use of peritoneal dialysis can improve early postoperative hemodynamics, but not necessarily mortality or other longer-term outcomes.
- Continuous veno-venous hemodialysis is a form of renal replacement therapy which can avoid rapid fluid and solute shifts associated with intermittent dialysis.

**Gastrointestinal and hepatic consequences of cardiac surgery in children**

**Splanchnic circulation**

**Mesenteric ischemia**

Bowel ischemia has been reported in adults following CPB [374–378]. Reported risk factors include age, atherosclerosis, heart failure, renal failure, use of vasoconstrictors, prolonged mechanical ventilation, and use of intra-aortic balloon counterpulsation [376,379–381]. Reports of mesenteric ischemia are very rare in the pediatric population. The single exception is gut ischemia seen after use of intra-aortic balloon pumps [382,383].

Necrotizing enterocolitis (NEC) is a common and devastating disease in the neonate. The pathogenesis of NEC is not clearly defined and is likely multifactorial with a complex interplay of altered intestinal microbiota, genetic polymorphisms, an immature intestinal barrier, and an exaggerated inflammatory response [384]. Primarily a disease of the premature infant, especially those with very low birth weight (i.e., < 1,500 g), 10% of infants affected are term or near-term neonates [385]. The incidence of NEC in the neonate with CHD ranges from 2.5% to 7.8% and this population accounts for most of the term infants with the disease [24,385–391]. In a large, retrospective analysis of term infants with CHD, McElhinney et al. found that diagnosis of hypoplastic left heart syndrome, truncus arteriosus, and aortopulmonary window were independently associated with NEC, with hypoplastic left heart syndrome conveying the highest risk [390]. In the Single Ventricle Reconstruction trial examining 549 neonates with single-ventricle physiology across 15 centers, the incidence of NEC was 2.5% as defined by pneumatosis intestinalis or free air on radiographs [392]. In a retrospective study of neonates who underwent a hybrid procedure (bilateral pulmonary artery banding, ductal stenting, possible atrial septal stent), the incidence of NEC was 11%, but neonates who developed NEC were significantly younger than hybrid neonates who did not develop NEC [388].

Necrotizing enterocolitis in the neonate with CHD may be a distinct disease process from that in the neonate without CHD. Vascular insufficiency rather than gut
immaturity could be the underlying cause of bowel ischemia in this population. Episodes of hypoperfusion, shock, and diastolic flow reversal in the aorta and superior mesenteric artery have been associated with NEC in the CHD population [393–397]. Mechanisms of intestinal ischemia may be related to physiologic steal that can occur in a parallel circulation. Clinical presentation tends to occur earlier in the neonate with CHD. In a retrospective look at 202 CHD patients with NEC, 48% were diagnosed before medical or surgical intervention on the cardiac lesion [398]. In the CHD population, NEC lesions are typically found in the colon, as opposed to lesions in children without CHD where the jejunum and ileum are most often affected [399]. Several studies have found that infants with CHD had decreased risk of perforation, strictures, need for a stoma, sepsis, and short gut syndrome compared with infants without CHD [390,398,400,401]. While mortality in neonates with CHD and NEC does not appear to be higher than that of cardiac neonates without NEC, morbidity is adversely affected. The diagnosis of NEC extends critical care and hospital length of stay significantly and increases the financial burden of care by $95,600 to $316,000 [402–404].

While a great deal has been learned about the pathogenesis of NEC in recent years, progress with respect to prevention and early detection has been slow, with radiographic imaging still the current standard. Gastric tonometry, abdominal ultrasound/Doppler, and a variety of biomarkers have not been successful in the early detection or prevention of NEC. Near-infrared spectroscopy (NIRS), a non-invasive technology that measures regional oxygen saturation, has been investigated as a possible early warning device for evolving tissue hypoxia. In 2011, Gay et al. described how abdominal NIRS probes were able to rapidly detect changes in mesenteric blood flow in an animal model of NEC [405]. A number of case reports describe changes in abdominal NIRS values in neonates with NEC [406, 407]. In an interesting study by Fortune et al., the authors found that the cerebral–splanchnic oxygen ratio (CSOR) could be more predictive of abdominal pathology than splanchnic NIRS alone. The authors demonstrated that a CSOR value of less than 0.75% predicted splanchnic ischemia with a positive predictive value of 0.75 and a negative predictive value of 0.96 [408].

In summary, neonates with CHD are at increased risk for NEC. Mortality does not appear to increase with this diagnosis in the CHD population, although hospital and critical care unit length of stay is prolonged. NIRS shows promise as a tool for early prediction of mesenteric ischemia but further investigation is needed.

Hepatic dysfunction
Acute hepatic failure has been described in the postoperative course of infants and children following cardiac surgery, but the relationship to the intraoperative course is uncertain. In a prospective observational study of 232 patients at a single institution, liver dysfunction was noted in 9.3% of patients as defined by a scoring system calculated using alanine amino transferase, total bilirubin, and prothrombin time. Shock in the postoperative period was the most important predisposing factor for hepatic dysfunction [409]. Previous retrospective studies link low cardiac output and elevated right atrial pressures as risk factors for hepatic failure [410,411].

Authors reviewed 16 cases of acute hepatic failure in the setting of MOF in children after cardiac surgery at a single institution spanning a 4-year period. Over this time period, 3.5% of patients developed MOF in the postoperative period. All patients underwent surgical correction using either deep hypothermic cardiac arrest (DHCA) or low-flow CPB (25% of initial flows). DHCA was always less than 60 minutes at 16°C. Duration of low-flow CPB was not described. Hepatic failure occurred in all 16 patients as defined by a serum glutamic oxaloacetic transaminase (SGOT) > 500 IU/L and a prothrombin time prolonged by at least 50%. SGOT values decreased after 48 hours in both survivors and non-survivors and normalized by 1 week in all survivors. Central venous pressures ranged from 3 to 17 mmHg and 8 to 17 mmHg at 4 and 24 hours, postoperatively. Hepatic perfusion pressures ranged from 35 to 67 mmHg and from 21 to 66 mmHg at 4 and 24 hours postoperatively. The most striking aspect of the perioperative course was the dose of epinephrine used. Doses ranged from 0.05 to 1.19 μg/kg/min with a mean of 0.43 μg/kg/min and were administered for a poorly contracting myocardium [412]. There are anecdotal reports of hepatic failure and MOF following cannula malposition of the inferior caval cannula in bicaval cannulation for CPB.

Endocrine response and pediatric cardiac surgery
The acute stress response to critical illness and surgical stress is the result of activation of the hypothalamic–pituitary–adrenal (HPA) [413] axis and sympathoadrenal system. During stress, the HPA axis typically responds by enhancing the release of cortisol (Figure 8.9). Approximately 85% of cortisol in the circulation is bound to corticosteroid-binding globulin (CBG) and 10% is bound to albumin. The remaining portion, free cortisol, is thought to be that which is biologically active [414]. Cortisol exerts its effects by binding to intracellular glucocorticoid receptors which play an important role in glucose metabolism, adrenergic receptor function, maintenance of endothelial integrity, and the systemic inflammatory response. CBG serves as a reservoir for protein-bound cortisol and is increasingly thought to play a role in facilitation of the activities of cortisol [415]. In critical illness, the HPA response to stress may be inadequate and result in persistent and profound inflammatory processes and hemodynamic insufficiency. It may result from either inadequate adrenal steroid production or decreased peripheral sensitivity to glucocorticoids. This dysfunction of the
The HPA axis in critical illness is usually temporary, can occur without structural insult to the hypothalamus, pituitary, or adrenal glands, and is termed critical illness-related corticosteroid insufficiency (CIRCI).

**Diagnosis of CIRCI**

Critical illness-related corticosteroid insufficiency, also known as relative adrenal insufficiency, has been defined as an inadequate level of serum cortisol relative to the severity of the patient’s illness and has been hypothesized to be associated with LCOS following cardiac surgery in children [416]. The diagnosis of CIRCI in children following congenital heart surgery remains difficult. Studies in this patient population report an incidence of 17–47%, but there is little agreement on the definition of CIRCI and the studies vary widely in the diagnostic criteria used [417–421]. In 2007, Menon et al. found no consensus among pediatric intensivists or endocrinologists as to the incidence or definition of adrenal insufficiency. Pediatric endocrinologists commonly use a cortisol level < 18.1 μg/dL following a corticotropin stimulation test, whereas pediatric intensivists made the diagnosis most commonly when a baseline serum cortisol was less than 5 μg/dL [422]. Additionally, there is substantial debate as to whether total cortisol (bound and unbound fractions) is an adequate reflection of the activity of the HPA axis when only the unbound fraction is thought to be biologically active. In a study whose purpose was to examine the effect of CPB on the HPA axis in children undergoing cardiac surgery, Wald et al. looked at the correlation of postoperative free and total cortisol levels and CBG levels with clinical outcomes. Interestingly, in their cohort of 51 patients, CBG levels varied widely and decreased from 28.8 ± 9.8 mg/L to 22 ± 8.4 mg/L following separation from bypass. Postoperative CBG levels < 19 mg/L correlated with increased length of stay and greater inotrope scores, even when adjusted for age and bypass duration. CBG levels were also independent predictors of inotrope score and fluid requirement in the first 24 hours postoperatively using multivariate analysis. This group of children exhibited
low cortisol levels following CPB (thought to be due to filtration or dilution), but all of them demonstrated a normal response to corticotropin stimulation. They did not find an association between postoperative baseline or post-stimulation levels of cortisol and clinical outcomes (length of stay, duration of mechanical ventilation, inotrope scores, or fluid requirements in the first 24 hours). In a prospective observational study of adrenal function in children undergoing Norwood palliation or interrupted arch with ventral septal defect (VSD) repair, Mackie et al. found that higher total cortisol levels correlated with lower cardiac index and higher atrial filling pressures at 48 hours postoperatively [418]. Although some postoperative patients have laboratory evidence of suspected CIRCI, there is conflicting evidence of a link to clinical outcomes in the first postoperative days [418–420,423].

Management of CIRCI
Annane et al. published a trial in which corticosteroid supplementation was found to reduce mortality in adult patients with septic shock [424]. Subsequently, a larger prospective trial of corticosteroid administration in adult septic shock failed to demonstrate the same mortality benefit [425]. Several studies have recently been published examining the effect of steroid supplementation in children following congenital cardiac surgery. While these studies are small and lack control groups, the administration of corticosteroids in the setting of suspected CIRCI in the postoperative period has been associated with improved hemodynamics [416,426]. Millar et al. reviewed the hemodynamic effects of corticosteroid administration. In those children who had undergone cardiac surgery, 41% demonstrated a greater than 20% increase in mean arterial pressure within 24 hours of steroid administration [427]. A positive hemodynamic response to steroids did not correlate with random total cortisol levels. A summary of the studies to date evaluating the effects of postoperative glucocorticoid administration are summarized in Table 8.3 [428].

Corticosteroid administration is associated with well-known risks. Infection, altered glucose metabolism, difficulty with wound healing, elevation in white blood cell count and adrenal suppression are among these risks. Certainly the short-term hemodynamic benefits may outweigh these risks in the most critically ill subset of patients following congenital cardiac surgery. Most of the studies examining the administration of corticosteroids in this patient population reported no increase in hyperglycemia or white blood cell count [416,417]. There is some recent evidence to suggest that an increase in mediastinal infection may be seen in those receiving perioperative steroids in low-risk surgical patients or in those with the highest number of days of corticosteroid exposure [23,429]. In a retrospective review of children less than 5 years of age undergoing cardiac surgery at a single center, cumulative days of corticosteroid exposure was independently associated with risk of infection [429]. Additionally, there is increasing concern regarding the negative long-term cognitive and neuromotor consequences of steroid exposure during the neonatal period [430]. Given the current data, it is important to carefully consider the routine treatment of low total cortisol with exogenous glucocorticoids.

Stress hyperglycemia
Collectively, hyperglycemia, insulin resistance, and glucose intolerance in the setting of acute illness are referred to as stress hyperglycemia [431]. Studies have shown both a strong correlation between stress hyperglycemia and poor outcomes and a linear relationship between the degree of hyperglycemia and disease severity [432,433]. Many clinicians and investigators have assumed this relationship is causal and critical care units have embarked upon protocols targeting various levels of glycemic control. However, studies examining strict glycemic control have not shown improved outcomes [434–436]. Several investigators have suggested that stress hyperglycemia is an adaptive response [437]. Stress hyperglycemia and insulin resistance are phylogenetically preserved responses that allow organisms to survive during stress [438,439]. The HPA axis, sympathoadrenal system, and proinflammatory cytokines work collectively to induce hyperglycemia during stress by increasing gluconeogenesis [431]. Glucose transport from the bloodstream to the cellular membrane depends on two mechanisms; a glucose concentration gradient across the interstitial space and a complex regulation among plasma membrane glucose transporters (GLUTs) that facilitate non-insulin-mediated glucose uptake across the lipid cell membrane [440]. In order for glucose to reach cells with reduced blood flow, stress hyperglycemia increases the glucose diffusion gradient and promotes glucose delivery to the cell. During infection, the regulation of GLUTs may play a role in redistributing glucose away from peripheral tissues and towards immune cells and the nervous system [437]. Hyperinsulinemia, severe acute hyperglycemia, and acute fluctuations in glucose concentrations have been implicated in endothelial cell dysfunction through an exaggerated oxidative stress response, which would support more moderate glucose levels versus tight glycemic control [431].

Outcome studies in the pediatric population
Hyperglycemia has been associated with perioperative morbidity and mortality in adult patients undergoing cardiac surgery [441,442]. In the pediatric population, retrospective studies linking hyperglycemia and outcome have yielded mixed results [306,443–447]. To date, three randomized controlled trials in the critically ill pediatric population have been published [448–450]. In 2009, a randomized controlled trial of 700 critically ill pediatric patients, three-quarters of whom were admitted after cardiac surgery, demonstrated that tight glycemic control (TGC) led to a reduction in vasoactive support, infection rate, ICU length of stay, and mortality compared with
### Table 8.3 Use of steroid therapy postoperatively in children with congenital heart disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Patients</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shore et al. [426]</td>
<td>Retrospective</td>
<td>&lt;1 year old 38% patients not postoperative</td>
<td>Compared patients treated with high-dose epinephrine with those who received high-dose epinephrine and hydrocortisone</td>
<td>Significant decrease in epinephrine within 12 hours of hydrocortisone. Hydrocortisone-treated patients required longer duration of inotropic support</td>
<td>Hydrocortisone-treated patients required longer duration of inotropic support</td>
</tr>
<tr>
<td>Suominen et al. [416]</td>
<td>Retrospective review</td>
<td>Neonates with LCOS who received hydrocortisone</td>
<td>Hydrocortisone for 5 days</td>
<td>Hydrocortisone significantly increased mean and systemic blood pressure, significant weaning of epinephrine within 24 hours of hydrocortisone</td>
<td>Hydrocortisone group had improved hemodynamics, less positive fluid balance, less body edema, improved oxygenation, shorter duration of mechanical ventilation</td>
</tr>
<tr>
<td>Ando et al. [417]</td>
<td>Prospective RCT</td>
<td>Neonates undergoing biventricular repair</td>
<td>Placebo vs. hydrocortisone for 72 hours followed by 4-day wean</td>
<td>Hydrocortisone had improved hemodynamics, less positive fluid balance, less body edema, improved oxygenation, shorter duration of mechanical ventilation</td>
<td>Hydrocortisone had improved hemodynamics, less positive fluid balance, less body edema, improved oxygenation, shorter duration of mechanical ventilation</td>
</tr>
<tr>
<td>Millar et al. [427]</td>
<td>Retrospective review of patients who received steroids for hypotension</td>
<td>35% of patients not postoperative</td>
<td>28.4% hydrocortisone, 17.6% dexamethasone, 3.9% methylprednisolone</td>
<td>41% had improvement in blood pressure, all patients with response survived. 20% mortality in non-responders</td>
<td>27.4% nosocomial infections, no GI bleeding</td>
</tr>
</tbody>
</table>

LCOS, low cardiac output syndrome; RCT, randomized controlled trial; GI, gastrointestinal.

Source: Green and Koch [428]. Reproduced with permission of Lippencott, Williams & Wilkins.

usual care [450]. Subset analysis of cardiac patients was not done. In the TGC group, investigators targeted glucose levels of 50–80 mg/dL in infants and 70–100 mg/dL in children aged 1–16 years. The prevalence of hypoglycemia was 25% (70 infants, 17 children), with possible symptoms of hypoglycemia noted in only three patients.

In 2012, the Safe Pediatric Euglycemia after Cardiac Surgery (SPECs) study published results of 980 patients younger than 36 months of age who underwent CPB. This was a two-center, randomized controlled trial with patients randomized into either a TGC (glucose levels of 80–110 mg/dL) or a standard care group. In order to minimize the risks of hypoglycemia, a subcutaneous sensor was inserted prior to sternal incision in the TGC group. This sensor was wirelessly paired with a continuous glucose monitor that displayed blood glucose levels every 5 minutes and alarmed if a glucose level dropped below manually set limits. Health care-associated infection, organ dysfunction, length of stay, and mortality were no different between the groups. The rate of hypoglycemia (<60 mg/dL) was 19% in the TGC group compared with 9% in the standard care group [448].

Most recently, Macrae et al. conducted a randomized controlled trial involving children admitted to 13 pediatric critical care units in England [449]. Patients between 36 weeks corrected gestational age and 16 years of age were eligible if they had an arterial catheter in place and were on mechanical ventilation and vasoactive drugs with an anticipated duration of treatment of at least 12 hours. A total of 1,369 children were assigned to either the TGC group with targeted glucose levels of 72–126 mg/dL or to the conventional treatment group in which glucose levels exceeding 216 mg/dL were treated until they fell below 180 mg/dL. Two-thirds of patients in this study were admitted to the critical care units following cardiac surgery and these patients underwent subset analysis. The 30-day primary outcome was the number of children alive and free from mechanical ventilation. Secondary outcomes included ICU and hospital length of stay, duration of mechanical ventilation and receipt of vasoactive drugs, need for renal replacement therapy, incidence of bloodstream infection, use of antibiotics for more than 10 days, number of red cell transfusions, Paediatric Logistic Organ Dysfunction (PELOD) score, rate of readmission to the ICU, and costs. TGC was associated with a smaller
proportion of patients receiving renal replacement therapy, yet authors did not report the significance of this in the cardiac population. No difference in other outcomes was found between the TGC and the conventional treatment groups in the cardiac population, yet hospital length of stay and costs were significantly lower in the non-cardiac population. Hypoglycemia occurred more often in the TGC group, with an incidence of 15.9% in the TGC group vs. 3.7% in the conventional treatment group.

The risk of hypoglycemia

Support for TGC in the pediatric cardiac population remains elusive and is probably due to the feared impact of hypoglycemia on the developing brain. Both hyper- and hypoglycemia have been associated with neurologic damage [451,452]. Although the major oxidative fuel of the brain is glucose, fetal and neonatal brains also have the capacity to oxidize ketone bodies, lactate, and perhaps amino acids [453–457]. With regard to neurocognitive and developmental outcomes, Mesotten et al. performed extensive neuropsychologic testing in the infants and children in the previously described study by Vlasselaers in which there was a prevalence of hypoglycemia of 25% [450]. At 3 years follow-up, these investigators found that TGC was associated with improved motor coordination and cognitive flexibility, and that hypoglycemia was not associated with worse neurocognitive outcome [458].

In conclusion, there are no clear guidelines for glycemic control following pediatric cardiac surgery and CPB. While hyperglycemia in the early postoperative period is universally seen, it is usually limited and can be attenuated by limiting glucose administration in the intraoperative and immediate postoperative periods [459–461]. Perhaps patients who have persistent hyperglycemia or who fail to convalesce as expected are the subset most likely to reveal the appropriate strategy of glycemic management in future studies [445].

Thyroid hormone

Thyroid hormone has a range of direct and indirect effects on the cardiovascular system that is mediated by genomic and non-genomic mechanisms [462–465]. Administration of triiodothyronine (T3) is associated with a decrease in systemic vascular resistance, an increase in the force of ventricular contraction, and more rapid diastolic relaxation [466–468].

Cardiac surgery, both with and without CPB, is associated with depression of thyroid hormone levels in adults and children. In 1978, Zucker et al. first measured low levels of thyroid hormone and low thyroid-stimulating hormone (TSH) in 19 children undergoing CPB, five of whom were on dopamine infusions that had previously been shown to depress TSH levels in healthy volunteers [469]. Bettendorf et al. measured plasma TSH, thyroxine (T4), T3, and thyroglobulin (Tg) in 132 children undergoing heart surgery before and up to 21 days postoperatively [470]. In addition to 85 patients placed on dopamine infusions, betadine solution was used for operative skin preparation and found to cause low thyroid levels in the neonate by Linder et al. [471]. Postoperative levels of TSH were lowest at day 1, while T3 and T4 were at their lowest on day 2. TSH typically increased to levels above those obtained preoperatively at day 5. Patients on dopamine infusions had the most striking changes in thyroid hormone levels. There was also a significant correlation between postoperative urinary iodine excretion and lowest T3 levels. Investigators also noted longer periods of mechanical ventilation and oxygen supplementation as well as higher inotrope use in patients with T3 levels < 0.6 nmol/L.

Of interest in these studies was the decrease in TSH levels suggesting changes at the hypothalamic–pituitary–thyroid axis. This pattern is also seen in non-thyroidal illness syndrome [22], once called “sick euthyroid syndrome,” a condition often seen in the setting of critical illness. It is unclear whether non-thyroidal illness syndrome is an adaptive response to critical illness that lowers oxygen consumption and catabolic burden or is maladaptive, potentially resulting in LCOS and organ failure. If maladaptive, could T3 infusions improve cardiovascular performance and improve outcomes?

In adults undergoing coronary bypass surgery, parental T3 repletion improves postoperative cardiac index and lowers the incidence of atrial fibrillation in select patients [472–478]. In pediatric patients undergoing cardiac surgery, three randomized, placebo-controlled trials of T3 supplementation demonstrated the safety of T3 infusions in the perioperative period but were underpowered to detect differences in clinical outcome [479–481]. Chowdhury et al. found no difference in inotrope scores, day on mechanical ventilation, or postoperative length of stay, although there was a trend in clinical improvement in neonates [480]. Mackie et al. performed a randomized, double-blind, placebo-controlled pilot trial of T3 in neonates undergoing the Norwood procedure or arch repair with VSD closure [481]. Primary endpoints were a composite clinical score composed of time until negative fluid balance, time until sternal closure, and time until first extubation. No differences were seen in the composite score between the treatment and placebo groups. The authors pointed out that the single variable of time until first negative fluid balance was shorter by half a day in the treatment group (P = 0.27). Bettendorf et al. did observe an improvement in cardiac index as measured by echocardiography [479]. A 2004 Conchrane review concluded that there was insufficient evidence regarding risk or benefit from T3 supplementation in the pediatric cardiac surgery population [482].

In 2010, results from the Triiodothyronine Supplementation in Infants and Children Undergoing CPB (TRICC) trial were published [483]. This study was a prospective, multicenter, double-blind, randomized, placebo-controlled trial examining T3 repletion vs. placebo in children less than
2 years of age undergoing cardiac surgery. No difference was found between the groups in the primary endpoint of time from aortic cross-clamp removal to extubation. However, subgroup analysis showed a significant interaction between age and treatment effects. In children less than 5 months of age, T3 repletion shortened time to extubation to a median of 55 hours, compared with 98 hours in the placebo group. In children greater than 5 months of age, there was a small but significant delay to extubation in the T3 group (20 hours in the T3 group, 16 hours in the placebo group). The risk of adverse events was similar between the two treatment groups.

In 2012, investigators published results of additional analysis from the TRICC trial examining the relationship between postoperative cytokine and T3 levels [484]. Studies in healthy adults had previously shown that infusion of recombinant IL-6 appeared to decrease T3 levels at 24 hours after the infusion [485]. In 1996, a study by Saatvedt and Lindberg demonstrated a significant inverse correlation between postoperative T3 and IL-6 levels in children following CPB [486]. In the TRICC subgroup, investigators found that postoperative cytokine levels were predictive of T3 levels at 6, 12, 24, and 72 hours. These authors suggested that preoperative screening of certain cytokines might help to risk-stratify patients at risk for prolonged intubation and determine which patients might benefit from postoperative T3 supplementation.

### Key Points: Gastrointestinal, Hepatic, and Endocrine Consequences of Cardiac Surgery in Children

- Hepatic dysfunction is noted in up to 9% of patients, with shock in the postoperative period being the most frequent risk factor.
- CIRCI can be observed after bypass; diagnosis is clinical and by ACTH stimulation test, and management is with stress dose corticosteroids.
- Hyperglycemia is common after bypass surgery and does not appear to have a major effect on short- or long-term outcomes in the cardiac population.
- Bypass is associated with decreased conversion of T4 to T3, and supplementation of T3 in infants is associated with shorter time to extubation.

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http://www.wiley.com/go/andropoulos/congenitalheart

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273. D’Alto M, Mahadevan VS. Pulmonary arterial hypertension associated with congenital heart disease. Eur Respir Rev 2012;21:328–37. This article provides excellent review of pulmonary arterial hypertension attributable to congenital cardiac disease. It includes an overview of the demographics, pathophysiology, and management of these patients, with a particular focus on patients with Down syndrome.


347. Taylor ML, Carmona F, Thiaagarajan RR, et al. Mild postoperative acute kidney injury and outcomes after surgery for congenital heart disease. J Thorac Cardiovasc Surg 2013;146:146–52. This was a retrospective cohort study of 693 children looking at the impact of mild acute kidney injury following surgery requiring CPB. They report an incidence of AKI lower than previously reported and found no association between mild renal injury and prolonged recovery. Moderate and severe kidney disease was independently associated with prolonged recovery.

353. Akcan-Arikan A, Zappitelli M, Loftis LL, et al. Modified RIFLE criteria in critically ill children with acute kidney injury. Kidney Int 2007;71:1028–35. This paper presents the pediatric modification of the RIFLE criteria for AKI. By these criteria, AKI during pediatric ICU admission was an independent predictor of ICU length of stay, hospital length of stay, and mortality independent of the Pediatric Risk of Mortality (PRISM II) score with an odds ratio of 3.0

358. Zappitelli M, Krawczeski CD, Devarajan P, et al. Early postoperative serum cystatin C predicts severe acute kidney injury following pediatric cardiac surgery. Kidney Int 2011;80:655–62. Cystatin C has been proposed as a marker of the efficiency of renal filtration which detects early identification of renal injury following CPB. In this multicenter prospective study of a cohort of 188 children (half under 2 years of age), early postoperative cystatin C was a better predictor of AKI than serum creatinine.

cohort study of 146 neonates and infants receiving peritoneal dialysis following cardiac surgery. Early dialysis was associated with a 46.7 decrease in the 30-day mortality when compared with later initiation of dialysis.

420 Wald EL, Preze E, Eickhoff JC, Backer CL. The effect of cardiopulmonary bypass on the hypothalamic-pituitary-adrenal axis in children. Pediatr Crit Care Med 2011;12:190–6. This is a prospective study in children undergoing surgery with CPB that found no correlation between low serum cortisol and compromised hemodynamics. Patients with higher free cortisol had increased length of stay, increased inotropic score, increased fluid requirement during the first 24 hours postoperatively, and longer duration of mechanical ventilation.
CHAPTER 9

Anesthetic and Sedative Neurotoxicity in the Patient with Congenital Heart Disease

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Introduction

The impact of anesthetics on the developing brain has been largely overlooked as a potential etiology of or contributor to neurologic injury acquired during cardiopulmonary bypass (CPB) [1]. Although various anesthetic agents have been used in a number of different animal models designed to study neurologic impairment following CPB, prior to 2001 there was little insight into the potential consequences of the agents themselves. The effect of specific anesthetics on neurologic outcome in the context of CPB was first explored by Kurth et al. and Loepke et al. [2–4]. These investigators compared the effects of different anesthetic strategies in neonatal piglet models of deep hypothermic circulatory arrest (DHCA) and low-flow CPB and demonstrated that the volatile anesthetic, desflurane, was able to limit brain injury in both flow states [3,4]. The results gave promise to the possibility of anesthesia-induced “neuroprotection” as a potential translational approach to infants and children undergoing open heart surgery.

However, in 2003, the concept of anesthetics being able to confer neuroprotection during development was challenged. In a landmark article by Jevtovic-Todorovic et al., commonly administered anesthetics were shown to be “neurotoxic” to the developing brain by causing widespread apoptosis [5]. Over the next several years, it became clear that the pediatric anesthesia community would be confronted with this provocative issue. As it is customary for an infant or young child with congenital heart disease (CHD) to be exposed to repeated and often prolonged periods of anesthesia, finding such adverse neurologic effects in a variety of animal models has raised serious concern.

Preclinical studies in animal and tissue culture models

Once the possibility of anesthesia-induced neurotoxicity came to light, investigators aimed to better define the issue. A series of in vitro investigations and animal studies soon followed [6–9]. The majority of the initial in vivo work...
focused on rodent models of anesthetic exposure during critical periods of development. Such investigations compared the effects of different anesthetics and have evolved by fine-tuning the various models studied in an effort to overcome potential confounders and more closely mimic the clinical scenario [10–13]. Furthermore, investigation has recently expanded to include the study of higher vertebrate mammals, including newborn non-human primates [14–18]. An advantage of in vivo models is that they allow for both short- and long-term determination of neurologic outcome [5,6,19]. Rodent models have focused on assessment of spatial learning and short- and long-term memory, while models utilizing larger animals employ more sophisticated scoring systems and scales to measure functional neurologic outcome [5,6,19].

Cell culture models offer controlled conditions of pH, temperature, oxygenation, and glucose and eliminate confounding variables intrinsic to animal investigation [8,9,20]. However, although able to assess for histologic injury, in vitro models do not always reflect the pathophysiology seen in the whole animal and have major limitations with regard to assessing functional outcome. For example, assessment of neurologic function in vitro is often limited to recording electrophysiology in hippocampal slices and reveals only a relatively short-lived phenomenon [21–23]. Tissue culture models, however, have been valuable in that they were able to confirm age- and duration-dependent effects of anesthetic exposure on neuronal death in a manner similar to what was shown in rodent models and helped to define the mechanism of neurotoxicity [8,9].

Although isoflurane has been the most widely studied anesthetic, virtually every volatile agent has been shown to cause neurotoxicity in developing neurons. Sevoflurane and isoflurane have both been found to induce neuronal cell death and impair long-term neurocognitive outcome to a similar degree; however, sevoflurane may not necessarily impair early or short-term memory [19,24–27]. Desflurane was found to be equivalent to isoflurane and sevoflurane in its ability to activate caspase-3, and exposure has been shown also to result in long-term memory impairment [28,29].

Regional distribution and cell-specific adverse effects of anesthetics have been observed in the developing brain and such vulnerability has been demonstrated to persist into young adulthood in areas such as the dentate gyrus and olfactory bulb [10]. Because the latter are regions of the brain that continue to undergo neurogenesis throughout development, the findings increased concern that the window of vulnerability for anesthetic neurotoxicity may be greater than previously realized [10]. However, there is some evidence demonstrating the potential for neuronal recovery, and environment may be key to both contributing to the acquired neurocognitive deficits and preventing long-term adverse effects following anesthetic exposure [30,31].

In addition to neurons, new evidence suggests that anesthetics can also cause injury in oligodendrocytes [14,15,17]. As such, anesthesia-induced apoptotic degeneration of oligodendrocytes was recently shown in the developing rhesus macaque brain. While neuronal susceptibility to anesthesia-induced toxicity corresponded to the peak in synaptogenesis, oligodendrocyte vulnerability to anesthetic exposure occurred during myelination [17]. Importantly, the distribution and extent of injury following anesthesia exposure differed in the fetal brain and the postnatal macaque brain. Because evidence suggests that the developing brain of infants with CHD parallels that of the premature infant and white matter injury can occur prior to or following CPB, it is quite possible that anesthetic exposure may contribute to or exacerbate neurologic impairment in this vulnerable cohort in the context of open heart surgery [32–37]. Such a concept will need to be addressed in future investigation.

The data regarding the neurotoxic effect of opioids are not as clear as those relating to volatile agents. However, there is a strong suggestion that certain opioids can induce apoptosis in developing neurons. For example, administration of a continuous fentanyl infusion resulted in a higher degree of caspase-3 labeling in specific brain regions of 5-day-old piglets compared with non-exposed controls [38]. Other studies have suggested a detrimental effect of morphine on neurons within the developing cortex and amygdala [21,39–40]. However, areas such as the hippocampus, which is important in memory formation, were relatively spared [21,39,40]. In contrast, recent investigation indicated that morphine had no impact on neuronal survival or differentiation in the postnatal rat brain [27]. As a high-dose opioid strategy is a common approach to the anesthetic care of infants and children with CHD, it is unclear if the current clinical paradigm results in or exacerbates anesthesia-induced neurotoxicity in such patients undergoing cardiac surgery. Thus, the data regarding opioids suggest that more investigation is necessary.

Although the utilization of ketamine as a sole anesthetic agent is not a common practice, it has become useful as an adjunct agent in pediatric cardiac anesthesia [41,42]. Ketamine has been shown to cause widespread apoptosis in the developing brain in several different rodent models [12]. Such ketamine-induced neurotoxicity has also been demonstrated in the fetal and neonatal rhesus macaque brain following exposure [16]. As with isoflurane, the fetal brain was much more vulnerable to neurodegeneration than the postnatal brain [16]. Furthermore, the pattern of neuronal loss after 5 hours of ketamine exposure differed between the two developmental ages [16]. Importantly, it has been observed that the apoptosis-inducing properties of ketamine can be attenuated with concomitant surgical stimulation [30]. It is important to note, however, that it is unknown if ketamine causes neurotoxicity in the human developing brain with or without surgery.

Compared with other commonly administered anesthetics, propofol has been less widely studied in preclinical neurotoxicity investigation [43]. Despite this, propofol-induced neuronal apoptosis has been shown to occur in both rodent and primate models [18,44].
Table 9.1 Anesthetic agents, receptor binding sites, neurodegenerative and neuroprotective effects in animal and tissue culture models

<table>
<thead>
<tr>
<th>Agent</th>
<th>Primary receptor binding site</th>
<th>Neurodegenerative effects</th>
<th>Neuroprotective effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GABA NMDA μ-opioid α₂-adrenergic</td>
<td>Neuroapoptosis Other Neuroprotective effects</td>
<td>Neuroprotection: anesthetic-induced neuroapoptosis Neuroprotection: excitotoxic neuronal death hypoxia–ischemia</td>
</tr>
<tr>
<td>Halogenated anesthetics</td>
<td>+++, +, – –</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>(sevoflurane, isoflurane, desflurane)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitrous oxide</td>
<td>–</td>
<td>–</td>
<td>NE</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Propofol</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>+</td>
<td>+</td>
<td>ND</td>
</tr>
<tr>
<td>Etomidate</td>
<td>+</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Chloral hydrate</td>
<td>+</td>
<td>++</td>
<td>ND</td>
</tr>
<tr>
<td>Ketamine</td>
<td>– – –</td>
<td>+++ +</td>
<td>+</td>
</tr>
<tr>
<td>Opioids</td>
<td>+++</td>
<td>+, NE</td>
<td>+</td>
</tr>
<tr>
<td>Dexametomidine</td>
<td>– –</td>
<td>++</td>
<td>NE</td>
</tr>
<tr>
<td>Xenon</td>
<td>– –</td>
<td>NE</td>
<td>NE</td>
</tr>
</tbody>
</table>

GABA, γ-aminobutyric acid; NMDA, N-methyl-D-aspartate; +, weak agonist or effect; ++, moderately strong agonist or effect; ++++, strong agonist or effect; –, weak antagonist or negative effect; – –, moderately strong antagonist or negative effect; – – –, strong antagonist or negative effect. NE, no effect; ND, no data. Source: data are from Loepke and Soriano [46].

Similar to isoflurane, the neurodegenerative effects caused by propofol were age-dependent with an age-specific cell death distribution pattern. In addition, as with isoflurane, propofol-induced oligodendrocyte injury occurred as well [17,18]. Interestingly, when compared with isoflurane, cell death induced by a 5-hour propofol exposure was only 25% of that observed in isoflurane-treated non-human primates [18]. It is unclear what impact this may have for the clinical scenario.

The majority of rodent models used to study anesthesia-induced neurotoxicity have permitted the animals to ventilate spontaneously. This has raised questions about the contribution of the respiratory depressant effects of anesthetics and the resultant impact of hypercarbia on neurodegeneration. To address this, carbon dioxide was administered to 7-day-old rats for 4 hours [13]. Hypercarbia alone induced cell death in the developing brain to a similar degree and distribution as isoflurane [13]. However, carbon dioxide-induced neurodegeneration did not result in impaired neurocognitive function [13]. These findings raise concern because carbon dioxide is often added to the CPB circuit due to changes in gas solubility with the use of hypothermia [45]. However, because there was no adverse effect of carbon dioxide on neurodevelopment, the significance of the rodent findings with regard to infants and children is not known. Adding to the complexity of this problem is the finding that many anesthetic agents, such as volatile anesthetics and ketamine, confer substantial neuronal protection in animal models of cerebral hypoxia–ischemia. A summary of anesthetic agents and their major receptor binding sites, and neurodegenerative and neuroprotective effects in animal and tissue culture models is presented in Table 9.1 [46].

**KEY POINTS: PRECLINICAL STUDIES IN ANIMAL AND TISSUE CULTURE MODELS**

- Virtually every anesthetic and sedative agent has been shown to induce widespread neurodegeneration in the developing brain in an age-dependent manner.
- Both neurons and oligodendrocytes are susceptible to apoptotic neurodegeneration.
- Both GABA- (volatile anesthetics, benzodiazepines, propofol, barbiturates) and NMDA-binding agents (ketamine, nitrous oxide) cause robust neuroapoptosis in animal and tissue culture models, including neonatal non-human primates.
- Opioids do not consistently cause neuroapoptosis to the same degree as GABA and NMDA agents.

**Mechanisms of anesthesia-induced neurotoxicity**

In 1989, MK801, an N-methyl-D-aspartate (NMDA) receptor antagonist, was shown to induce histopathologic
toxicity in the mature rodent brain [47]. Subsequently, a number of studies demonstrated that both NMDA receptor inhibitors and γ-aminobutyric acid-A (GABA)α receptor agonists were capable of triggering apoptosis in the younger, developing brain [48,49]. These findings prompted investigation to assess whether or not other agents with similar mechanisms of action could deleteriously affect the brain during critical times in development. As such, ethanol, a well-known NMDA antagonist and GABA mimetic agent, was evaluated and shown to induce robust neuronal apoptosis in the developing brain [48]. This toxic response was attributed to the combination of its effects on both receptor types and was proposed as an explanation for the ethanol-induced neurodevelopmental abnormalities seen with fetal alcohol syndrome [50,51].

Because the majority of anesthetic agents possess NMDA antagonist and/or GABA agonist properties, investigators began to rigorously explore the effect of such pharmacologic agents on neuronal programmed cell death [52]. Over a decade of work has since revealed that a variety of commonly used anesthetics cause widespread apoptotic neurodegeneration in various brain regions during development. Although the phenomenon of anesthesia-induced neuronal apoptosis is now a universally accepted concept and has been demonstrated in a host of different mammalian animal species, the exact mechanisms have not been fully elucidated [51]. However, it has become clear that, downstream in the process, anesthesia-induced neurotoxicity is mediated by the mitochondrial pathway of apoptosis followed by activation of the death receptor pathway and neurotrophic factor-activated pathways (Figure 9.1) [50,53]. Here we will review the different pathways known to become activated or dysregulated by various anesthetic agents, resulting in widespread apoptosis in the developing brain.

**Mitochondria, oxidative stress, and the intrinsic apoptosis pathway**

The major role of each mitochondrion is to generate cellular energy via oxidative phosphorylation. However, mitochondria also have a variety of other regulatory functions that are important for both cell survival and cell death. One example is the intrinsic apoptosis pathway, which results in organized and controlled cell “suicide” (Figure 9.1) [54]. The pathway is activated when cytochrome c is released from mitochondria into the cytosol. Once released, cytochrome c forms the apoptosome along with the apoptotic protease activating factor 1 (APAF-1) in the presence of deoxyadenosine triphosphate (dATP) and adenosine triphosphate (ATP) [54–57]. The apoptosome complex then binds and activates procaspase-9 [54–57]. Activated capase-9, in turn, activates capase-3, resulting in deoxyribonucleic acid (DNA) fragmentation and cell death. [56,57].

Cytochrome c, located in the mitochondrial intermembrane space, normally functions as the mobile electron carrier between complexes III and IV in the respiratory chain during oxidative phosphorylation. However, cytochrome c can exert peroxidase activity and, when bound to cardiolipin (CL) on the inner mitochondrial membrane, can oxidize CL to hydroperoxycardiolipin (CL-OOH) [58]. This important upstream event mobilizes cytochrome c from the inner membrane and facilitates its release following a pro-apoptotic stimulus. Translocation of B-cell lymphoma-2-associated X protein (Bax) from cytosol to mitochondria permeabilizes the outer mitochondrial membrane and permits the release of cytochrome c from mitochondria into the cytosol [56,57]. Membrane permeabilization can be inhibited, however, when the anti-apoptotic proteins, B-cell lymphoma-2 (BCL-2) and B-cell lymphoma-extra large (BCL-xL) bind to and interact with Bax [59,60].

Exposure to isoflurane has been shown to increase mitochondrial translocation of Bax and reduce BCL-2 levels in the developing brain [61]. These pro-apoptotic effects promote cytochrome c release into cytosol, resulting in the activation of caspase-9 and -3 following anesthetic exposure [60]. Providing some insight into upstream mechanisms, isoflurane has also been found to increase cytochrome c peroxidase activity in the forebrain of newborn mouse pups [62]. Because cytochrome c requires hydrogen peroxide to oxidize CL, isoflurane-induced increases in peroxidase activity probably occur due to oxidative stress [63,64]. In support of this, a number of anesthetic agents, such as isoflurane, sevoflurane, and propofol, have been shown to increase free radical production in the developing brain [65,66]. Even under normoxic conditions, exposure to these anesthetics has been demonstrated to result in reactive oxygen species (ROS) and reactive nitrogen species generation in developing neurons, hippocampus, subiculum, and thalamus [67–69]. Oxidative stress from anesthetics can also lead to membrane lipid peroxidation, mitochondrial damage, and disruption of mitochondrial integrity [51].

Using knockout mice and newborn rats, investigators have shown that anesthetic-induced cytochrome c release is dependent upon Bax and reduced levels of the anti-apoptotic mediator, BCL-xL [70]. Although it is unknown how Bax translocation is triggered following anesthetic exposure, studies suggest involvement of mitogen-activated plasma kinase systems and the extracellular signal-regulated protein kinase (ERK) pathway [70]. For example, ketamine and propofol have both been shown to reduce phosphorylated ERK1/2 and protein kinase B (Akt) levels in 5-day-old mouse pups [52]. However, more than one survival pathway may be involved [52].

**The extrinsic apoptosis pathway**

The extrinsic apoptosis pathway becomes activated following binding of various apoptosis-inducing ligands to their respective death receptors (Figure 9.1) [54]. Pro-apoptotic ligands such as tumor necrosis factor-alpha (TNF-alpha), FasL (TNF superfamily member 6 ligand),
Figure 9.1 The intrinsic and extrinsic pathways of apoptosis. The intrinsic pathway involves translocation of B-cell lymphoma-2-associated X protein (Bax) from cytosol to mitochondria to permeabilize the outer mitochondrial membrane and permit release of cytochrome c from mitochondria into the cytosol. Upstream, cytochrome c exerts peroxidase activity and oxidizes cardiolipin (CL) to hydroperoxycardiolipin (CL-OOH) in the presence of hydrogen peroxide (inset). This mobilizes cytochrome c from the inner membrane and facilitates its release once the outer membrane is permeabilized. Once released, cytochrome c forms the apoptosome along with apoptotic protease activating factor 1 (APAF-1). The apoptosome complex then binds and activates procaspase-9 which, in turn, activates caspase-3. Membrane permeabilization can be inhibited by B-cell lymphoma-2 (BCL-2) and B-cell lymphoma-extra large (BCL-xL). The extrinsic apoptosis pathway becomes activated following binding of death receptor ligands to their receptors. This recruits Fas-associated death domain (FADD) which, in turn, recruits and activates procaspase-8. The targets of specific therapeutic agents are demonstrated. Green arrows indicate activation, red bars indicate inhibition. TNFα, tumor necrosis factor-alpha; BDNF, brain-derived neurotrophic factor; TrkB, tropomyosin receptor kinase B; EPO, erythropoietin; Akt, protein kinase B; Erk, extracellular signal-regulated protein kinase. (Source: data are from Almasieh et al. [149] and Perier et al. [150].)

and TNF-related apoptosis-inducing ligands (TRAILs) can initiate the pathway [54]. Activation of death receptors results in recruitment of the intracellular adaptor Fas-associated death domain (FADD) which, in turn, recruits procaspase-8 [54]. This results in caspase-8 activation and subsequent activation of caspase-3 [54]. Exposure to isoflurane along with nitrous oxide and midazolam was shown to upregulate forebrain Fas and activate caspase-8 in the parietal cortex and occipital cortex within 6 hours of exposure in 7-day-old rats, indicating activation of the extrinsic pathway [53]. Interestingly, the intrinsic apoptosis pathway also became activated in the forebrain of the same animals within 2 hours of exposure, a much earlier time point [53]. It was suggested that the timing of onset of mitochondrial pathway activation was related to the rapid decrease in BCL-xL following anesthesia exposure, while activation of the extrinsic pathway was somewhat delayed due to the dependence on expression and upregulation of the Fas protein [53]. Furthermore, as activated caspase-8 was not widespread and was limited to certain areas of the developing brain, investigators concluded that the death receptor pathway of apoptosis probably does not play a major role in the manifestation of anesthesia-induced neurotoxicity [53].

Brain-derived neurotrophic factor

Neurotrophins are a group of growth factors known to promote neuronal survival, differentiation, and synaptic plasticity [71]. Brain-derived neurotrophic factor (BDNF), a neurotrophin found in abundance in the developing brain, binds to two different classes of receptors [71].
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Following binding of BDNF to the first receptor type, the tropomyosin receptor kinase B (TrkB) receptor, Akt (the most widely recognized serine/threonine kinase known to promote cell survival) becomes activated and ultimately phosphorylated (Figure 9.1) [51,72]. However, binding of BDNF to the second receptor type, the p75NTR neurotrophic receptor (p75NTR), reduces synaptogenesis, withdraws dendritic spines, and leads to neuronal apoptosis [51,71].

Seven-day-old rats exposed to 6 hours of isoflurane with nitrous oxide and midazolam demonstrated a decrease in BDNF in the developing thalamus [71]. This decrease was associated with a reduction in Akt activity and an increase in caspase-9 and -3 activation [71]. This pro-apoptotic response was likely mediated via the Trk-dependent apoptotic pathway. On the other hand, BDNF levels were paradoxically increased in the cerebral cortex following exposure to the same anesthetic cocktail [71]. However, as with the thalamus, Akt activity in the cortex was reduced and caspase-9 and -3 activities were increased [71]. This cortical response is best explained by the p75NTR Trk-independent pathway which is known to be able to override the Trk dependent survival pathway [71]. Taken together, the overall BDNF findings can be explained by the activation of both pathways and provides evidence of BDNF-mediated apoptosis as a mediator of anesthesia-induced neurotoxicity.

**Cell age-specific vulnerability**

The immature brain is uniquely vulnerable to the phenomenon of anesthesia-induced neuronal apoptosis. Furthermore, certain neurons undergo cell death following anesthetic exposure while adjacent cells remain seemingly unaffected. Until recently, no explanation had been put forward to explain these findings. In a very elegant study, using birth-dating, Hofacer et al. demonstrated that anesthetic vulnerability relates more to the age of the neuron and not the age of the organism [73]. The investigators showed that most of the dentate granule cells that underwent isoflurane-induced neurodegeneration were young and relatively immature [73]. Vulnerability to anesthetic exposure peaked approximately 2 weeks after cells were born [73]. The authors extended their evaluation to neurons within the olfactory bulb, which undergo neurogenesis into adulthood. As predicted, they found that adult-generated neurons are just as susceptible to anesthesia-induced apoptosis, indicating that it is the stage of neuron maturation, rather than the chronological age of the host, that may dictate which cells die[73].

**Summary of human cardiac cohorts**

Over the past two decades, perioperative survival in neonatal cardiac surgery has increased to greater than 90%, and neurodevelopmental outcomes in CHD have become an important focus [74]. Larger numbers of patients with increasingly complex cardiac lesions are repaired or palliated, and it has become evident that neurodevelopmental problems are common in this patient population [75]. With refinements in surgical, bypass, anesthetic, and intensive care approaches, gross neurological deficits such as hemiparesis, clinical seizures, coma, and choreoathetosis are now only infrequently observed. However, 30–50% of neonates undergoing complex cardiac surgery have deficits in general intelligence, gross and fine motor function, and receptive and expressive language when tested later during infancy [76].

At age of school entry, when multiple domains can be tested, defects in cognition, executive function, memory, language, mathematics, and visual-motor integration are also significantly more common in children who have undergone heart surgery than in the general population [77]. Reported associations with worse neurodevelopmental outcomes include many non-modifiable factors, such as chromosome abnormalities, brain immaturity, single-ventricle lesions, and parental education and intelligence [75,78,79]. Modifiable factors associated with lower neurodevelopmental outcome scores include magnetic resonance imaging (MRI) brain injury, low regional cerebral oxygen saturation, prolonged DHCA vs. use of regional cerebral perfusion during aortic arch reconstruction, and extreme hemodilution during bypass [80–83]. Multivariable models have explained less than 50% of the variation in outcomes [80,81,84]. This lack of robust models emphasizes the myriad factors, some recognized but many not known, that may influence neurodevelopmental outcomes in CHD. The reader is referred to Chapter 11 for a complete discussion of neurological monitoring and outcomes.

The many unknown risk factors for adverse neurodevelopmental effects in CHD have led to a search for additional variables to study in order to improve outcomes in this largest group of neonates and infants undergoing surgery and other invasive procedures in the first year of life (totaling around 9,200 patients annually in the US) [85]. The growing body of animal model data reviewed here, as well as concerns raised by retrospective and epidemiological studies in non-cardiac anesthetics in children, have led to the conclusion that anesthetic exposure to GABA and NMDA binding agents in infant
cardiac surgery should be studied. Conversely, volatile anesthetic agents and ketamine exhibit neuroprotective properties in animal models of cerebral ischemia caused by low-flow CPB and inflammatory pain, respectively \[46,87\]. The many confounding variables in the infant cardiac surgical patients complicate the study of this population. Because of the often large exposure to anesthetic and sedative agents, and the ability to modify practice, anesthetic technique is an important area to assess in relation to whether modifications in drugs or doses could lead to improved neurodevelopmental outcomes.

Patients with CHD frequently experience a larger exposure to anesthetic and sedative agents during young infancy than other groups of neonates or infants undergoing surgery. Early neonatal surgery is currently the standard of care in most institutions, a time of maximal vulnerability to potential anesthetic neurotoxicity. Prolonged operating room times and intensive care unit stays, and repeated anesthetic and sedative exposure for additional surgery, cardiac catheterization, non-cardiac surgery, and other diagnostic studies such as cardiac MRI are common in this population, particularly in patients with single-ventricle lesions. Cumulative exposure to multiple GABA and NMDA binding agents is frequently large, in terms of drug dose, days of exposure, and “area under the curve” for exposure, e.g. MAC-hours. Tolerance to opioids and benzodiazepines may develop, with additional adverse effects on neurodevelopmental outcomes \[88\]. In addition, there is significant variability between institutions in anesthetic approach, especially with regard to opioid and volatile anesthetic dosing, and intraoperative benzodiazepine use for neonatal cardiac surgery. Anesthetic technique is a potentially modifiable factor within the standard of practice among cardiac anesthesiologists and as such could be an important approach to study for improving neurodevelopmental outcomes.

Until recently there were no published data that specifically assessed anesthetic exposure and neurodevelopmental outcomes in CHD. Guerra et al. retrospectively assessed anesthetic and sedative exposure for subjects enrolled in a prospective observational study of neonates and young infants undergoing complex cardiac surgery \[89\]. Ninety-five infants who had surgery at less than 6 weeks of age were studied: 48% underwent arterial switch operation, 24% Norwood stage I palliation, 12% total anomalous pulmonary venous return repair, and 15% had other two-ventricle complete repairs. Patients with chromosome abnormalities were excluded. Subjects underwent neurodevelopmental assessment at age 18–24 months, utilizing the Bayley Scales of Infant Development (BSID). The BSID is a widely used standardized test of cognitive, motor, and language functioning for infants less than 3.5 years of age. Scores are scaled to a population mean of 100, with a standard deviation (SD) of 15. Guerra et al. assessed anesthetic and sedative exposure in the first 6 weeks, and determined the percentage of subjects with neurodevelopmental scores > 2 SDs below the population norms on the BSID version II or III, denoting a significant delay. In the normative reference population, 3.5% are more than 2 SDs below the mean, but Guerra et al. determined that 7% and 11% of their subjects were below 2 SDs for the Mental Development Index and Psychomotor Development Index, respectively. In addition, 31% of the subjects were below the 15th percentile level for vocabulary delay. All patients in the study received volatile agents, benzodiazepines, and opioids, with a mean of 15–16 days exposure to the latter two classes of drugs. In addition, 73% received chloral hydrate and 56% received ketamine.

However, when a multivariable analysis was performed, anesthetic and sedative dose had no association with neurodevelopmental outcome scores. Significant associations were demonstrated with days of mechanical ventilation, older age at surgery, lowest PaO₂, use of circulatory arrest, and maternal education. In a follow-up study of the same cohort of patients tested at age 4 years, these investigators did find a small, but significant, association with greater number of days receiving chloral hydrate and lower performance intelligence quotient, and an association between larger benzodiazepine dose and lower visual-motor integration scores \[90\]. This study cohort is limited by the fact that only the first 6 weeks of anesthetic and sedative data were collected, and the change from BSID II to BSID III mid-cohort prevented assessment of continuous neurodevelopmental outcome variables at 18–24 months. Nonetheless, the finding of an association with larger GABA binding agent exposure and lower scores on several domains of continuous neurodevelopmental outcome variables at age 4 years after multivariable adjustment is an important one.

Andropoulos et al. reported the association between anesthetic and sedative exposure, MRI brain injury, and neurodevelopmental outcomes in 59 neonates undergoing cardiac surgery enrolled in prospective observational cohort studies \[91\]. Forty seven percent of these patients had hypoplastic left heart syndrome (HLHS) or other single-ventricle lesion and underwent Norwood stage I palliation, 33% had dextrotransposition of the great arteries and underwent arterial switch operation, and 11% had a ventricular septal defect with aortic arch hypoplasia or other two-ventricle-type lesions and underwent complete repair. Anesthetic and sedative data had been collected prospectively in the neonatal period. All remaining anesthetic and sedative exposure data were collected retrospectively from the neonatal period through the first 12 months of life, at which time the BSID III was administered. A multivariable analysis of anesthetic exposure, magnetic resonance brain injury, and other important covariates was performed.

Mean volatile anesthetic agent (VAA) MAC-hour exposure was 4.4 ± 3.1, with five subjects having 10–15 MAC-hours exposure. The mean fentanyl equivalents exposure was 553 ± 585 g/kg, and benzodiazepine exposure 14.3 ± 25.0 mg/kg. A significant association was demonstrated between larger VAA exposure and lower cognitive score on the BSID III (Table 9.2). Weak associations were found between larger benzodiazepine exposure...
and higher cognitive score, and larger opioid exposure and higher cognitive and language score. The most consistent association in this study was between longer intensive care unit stay and lower scores in cognitive, language, and motor domains. The final multivariable model explained 23–33% of the variation in BSID III scores.

The published data from these two cohorts of CHD patients from different institutions underscore several important findings as the contribution of anesthetic technique and dose to neurodevelopmental outcome is assessed. First, the number of confounding variables is significant, and despite multivariable adjustment, the models of anesthetic exposure still explain only about one-third or less of the variation in neurodevelopmental outcomes. The total number of patients reported in these studies is small (154), and this makes multivariable analysis methods difficult, as the likelihood of a false-positive (type I) error increases. Retrospective anesthetic data collection has well-known limitations, and potentially more accurate computerized anesthetic records were utilized for only a few patients in these studies. Finally, two different versions of the BSID were used in these cohorts, making comparisons difficult among subjects receiving different versions of this test because of their substantial differences.

However, both studies did find associations between larger anesthetic and sedative exposure, particularly the GABA binding agents, and lower neurodevelopmental outcome scores at 12 and 48 months of age. As such, these studies support the conclusion that anesthetic technique could potentially affect neurodevelopmental outcomes in CHD patients. These studies in no way establish a causal relationship, but are useful to serve as potential hypothesis-generating studies for further research.

### Key Points: Human Cardiac Cohorts

- Children with CHD have lower neurodevelopmental outcome scores compared with the general population.
- Two small published cohort studies have shown an association between larger anesthetic and sedative exposure, particularly the GABA-binding agents, and neurologic impairment in this vulnerable cohort.

### Experimental Therapy in Preclinical Studies

As evidence has emerged to indicate an association between anesthesia exposure and cognitive and behavioral disorders in young children, a number of investigators have begun to explore potential therapeutic and preventative strategies in an effort to protect the developing brain from anesthesia-induced neurotoxicity. Many of these experimental interventions have demonstrated benefit in preclinical animal studies. If, in the future, anesthetics are shown to definitively cause neurodegeneration in humans, then translation of such clinically applicable therapies and approaches could become important for the safety and well-being of infants and children who require anesthesia.

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**Table 9.2** Forward stepwise multivariable analysis final model of perioperative associations with Bayley Scales of Infant Development III (BSID III) cognitive, language, and motor composite scores at age 12 months

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Cognitive P-value</th>
<th>Coefficient (95% CI)</th>
<th>Language P-value</th>
<th>Coefficient (95% CI)</th>
<th>Motor P-value</th>
<th>Coefficient (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative MRI injury†</td>
<td>0.548</td>
<td>–2.04 (–8.80, 4.72)</td>
<td>0.179</td>
<td>–4.15 (–10.27, +1.96)</td>
<td>0.390</td>
<td>–3.20 (–10.61, +4.21)</td>
</tr>
<tr>
<td>New postoperative MRI injury†</td>
<td>0.029*</td>
<td>–6.85 (–13.36, –0.34)</td>
<td>0.020*</td>
<td>–6.96 (–12.79, –1.13)</td>
<td>0.053</td>
<td>–6.95 (–14.00, +1.13)</td>
</tr>
<tr>
<td>MAC-hours VAA‡</td>
<td>0.028*</td>
<td>–1.26 (–2.37, –0.14)</td>
<td>0.056</td>
<td>–0.95 (–1.93, +0.03)</td>
<td>0.455</td>
<td>–0.47 (–1.71, +0.78)</td>
</tr>
<tr>
<td>Fentanyl equivalents (μg/kg)‡</td>
<td>0.025*</td>
<td>+0.01 (+0.01, +0.28)</td>
<td>0.007*</td>
<td>+0.13 (+0.01, +0.02)</td>
<td>0.278</td>
<td>+0.01 (–0.01, +0.02)</td>
</tr>
<tr>
<td>Benzodiazepine equivalents (mg/kg)‡</td>
<td>0.048*</td>
<td>+0.14 (+0.01, +0.28)</td>
<td>0.643</td>
<td>–0.27 (–1.5, +0.09)</td>
<td>0.406</td>
<td>+0.06 (–0.09, +0.22)</td>
</tr>
<tr>
<td>ICU LOS (days)</td>
<td>0.001*</td>
<td>–0.48 (–0.75, –0.21)</td>
<td>0.001*</td>
<td>–0.41 (–0.65, –0.17)</td>
<td>0.021*</td>
<td>–0.35 (–0.64, –0.06)</td>
</tr>
<tr>
<td>Preoperative mean rSO₂ (%)</td>
<td>0.041*</td>
<td>+0.45 (+0.02, +0.89)</td>
<td>– – –</td>
<td>– – –</td>
<td>0.018*</td>
<td>0.59 (0.11, 1.07)</td>
</tr>
<tr>
<td>Aprotinin administration</td>
<td>– – –</td>
<td>– – –</td>
<td>– – –</td>
<td>– – –</td>
<td>– – –</td>
<td>– – –</td>
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<tr>
<td>Abnormal chromosomes</td>
<td>– – –</td>
<td>– – –</td>
<td>– – –</td>
<td>– – –</td>
<td>– – –</td>
<td>– – –</td>
</tr>
<tr>
<td>R² of model</td>
<td>0.36</td>
<td>0.54 (0.01, 1.07)</td>
<td>0.23</td>
<td>0.33</td>
<td>0.99</td>
<td>0.96</td>
</tr>
</tbody>
</table>

MRI, magnetic resonance imaging; MAC, minimum alveolar concentration; VAA, volatile anesthetic agent; ICU, intensive care unit; LOS, length of stay; rSO₂, regional cerebral oxygen saturation; CI, confidence interval. ¶, covariates forced into final model. *, covariates with significant associations with BSID III neurodevelopmental testing domains (P < 0.05); – – –, no association in final model. Additional covariates tested included birth weight, gestational age, single- vs. two-ventricle cardiac lesion; maternal intelligence, hospital LOS, erythropoietin administration, MRI brain maturity score, bypass time, regional cerebral perfusion time, deep hypothermic circulatory arrest time, mean intraoperative and postoperative rSO₂, and mean inotrope score.

Source: Andropoulos et al. [91]. Reproduced with permission of Wiley.
and sedation at critical times during development. Here we will review the various experimental strategies that have been shown to provide some level of protection to the developing mammalian brain from anesthesia-induced neurotoxicity.

Anesthetic preconditioning
Preconditioning is the process by which tissue protection is conferred following brief exposure to a mild stimulus leading to temporary resistance to subsequent severe stimuli or injury [92]. Ischemia, hypoxia, hypothermia, and certain types of medications have all been successfully utilized to precondition a variety of tissues, including the brain [93]. Preconditioning with volatile anesthetic agents, such as isoflurane, sevoflurane, and halothane, has been shown to limit the degree of brain injury in a number of animal models of cerebral ischemia [93]. Based on this knowledge, investigators tested whether or not brief exposure to a low concentration or dose of anesthetic could attenuate the apoptotic response caused by longer, more toxic anesthetic exposures. In cell culture, primary cortical neurons were shown to be protected from anesthesia-induced neurotoxicity in a dose-dependent manner following preconditioning with up to 2.4% isoflu-rane for 1 hour prior to a 24-hour isoflurane exposure [94]. In other work, pretreatment with 70% xenon for 2 hours prevented nitrous oxide and isoflurane-induced apoptosis in the hippocampus and cortex of 7-day-old rats 24 hours following preconditioning [95]. Such pretreatment with xenon was also shown to preserve neurocognitive function in preconditioned animals [95]. Another investigation demonstrated that administration of low-dose ketamine 1 day prior to injection of a neurotoxic ketamine dose abrogated neurodegeneration in the developing rodent brain [51]. Injection of 5 mg/kg ketamine 24 hours prior to injection of 20 mg/kg ketamine decreased the number of activated caspase-3-positive cells in different brain regions of 7-day-old rats [51]. Although the exact mechanisms of anesthetic preconditioning are not known, preliminary data suggest modulation of the BCL-2/Bax ratio, down-regulation of the tumor suppressor transcription factor, P53, generation of ROS, induction of mild endoplasmic reticulum stress, and activation of the adenosine A1 receptor, protein kinase C, and ATP-dependent potassium channels as possible contributors to neuroprotection (Figure 9.1) [94,95].

Dexmedetomidine
Dexmedetomidine is a central α2-adrenoceptor agonist with sedative, analgesic, and sympatholytic properties [96]. During brain development, α2 adrenoceptors are believed to play a role in activating survival pathways in the central nervous system [97]. In an adult model of cerebral ischemia, dexmedetomidine was shown to upregulate the anti-apoptotic proteins, mouse double minute 2 homolog (mdm2) and BCL-2 [98]. Furthermore, α2-adrenoceptor agonists upregulate the expression of BDNF, increase the content of phosphorylated cAMP response element binding protein, and enhance ERK survival signaling (Figure 9.1) [98,99]. Because dexmedetomidine has been shown to act as a neuroprotectant in a variety of settings of experimental neuronal injury, investigators tested whether activation of α2 adrenoceptors could prevent anesthesia-induced neurotoxicity. As such, intraperitoneal injection of dexmedetomidine limited isoflurane-induced activation of caspase-3 in a dose-dependent manner in the hippocampus, thalamus, and cortex of 7-day-old rats exposed to 6 hours of 0.75% isoflurane [97]. Furthermore, treatment with dexmedetomidine prevented isoflurane-induced long-term memory impairment [97]. The authors concluded that, based on their findings, dexmedetomidine could become an important preventative therapy if anesthesia-induced neurotoxicity is found to occur in the human clinical scenario [97].

Erythropoietin
Erythropoietin (EPO) is a growth factor that is well known for its effect on erythropoiesis [100]. However, it has become widely recognized that EPO and the EPO receptor are also expressed in the nervous system [100]. Expression peaks during brain development and EPO synthesis has been shown to be upregulated in the mature brain following hypoxia, traumatic injury, subarachnoid hemorrhage, and stroke [100]. Expression of endogenous EPO has been shown to be neuroprotective and involves activation of the phosphatidylinositol 3-kinase (PI3K)/Akt, Ras/ERK1/2, and nuclear factor-κ-B pathways following binding to and EPO-mediated phosphorylation of its receptor (Figure 9.1) [100]. In addition, exogenously administered EPO crosses the blood–brain barrier, stimulates neurogenesis, induces neuronal differentiation, activates neurotrophic signaling, and exerts anti-apoptotic, antioxidant, and anti-inflammatory properties [100]. Isoflurane has been shown to suppress EPO transcription in the mouse brain in a concentration-dependent manner and in primary astrocyte cell culture under hypoxic conditions [101]. However, administering 50,000 IU/kg EPO subcutaneously successfully attenuated neurodegeneration induced by a 6-hour exposure to 1% isoflurane in 7-day-old rats and prevented acquired learning deficits [102]. A phase I/II randomized, placebo-controlled trial of EPO for neuroprotection in neonates undergoing complex cardiac surgery was recently published [103]. Intravenous EPO 500 or 1000 IU/kg in three perioperative doses was assessed for safety, and for preliminary indication of efficacy for improving neurodevelopmental outcomes, with 12-month BSID III as the primary outcome. Median isoflurane exposure during neonatal surgery was 1.7 MAC-hours. No neurodevelopmental differences were found in the 42 subjects evaluated, nor were any differences detected in safety outcomes. The authors concluded that besides lack of power to definitively answer the question of EPO neuroprotection in this population, ideal future study
design should include a more prolonged course of EPO dosing at the higher range, especially preoperatively. Thus, exogenous EPO may represent a clinically relevant therapeutic agent to potentially target anesthesia-induced neurotoxicity in the future.

**Lithium**

Regulation of glycogen synthase kinase-3β (GSK-3β) activity is important for memory formation [104,105]. Inhibition of GSK-3β via phosphorylation has been shown to enhance long-term memory in hippocampus-dependent tasks, while constitutively active GSK-3β has been shown to impair memory formation [106]. In experimental work, sevoflurane inhibited phosphorylation of GSK-3β in the hippocampus of rats exposed to various concentrations for 2 hours and impaired memory retention in exposed animals [106]. Lithium chloride, a well-known inhibitor of GSK-3β, has been shown to protect against medication and hypoxia–ischemia-induced neuronal apoptosis in the developing brain [107]. In a recent study, intraperitoneal injection of 100 mg/kg of lithium prevented sevoflurane-induced dephosphorylation of GSK-3β in rats and blocked the deleterious effects of sevoflurane on memory consolidation [106]. The findings suggest that the GSK-3β pathway may be important as a potential target for therapy designed to prevent anesthesia-induced impairments in memory and learning.

**Vitamins, anti-inflammatory agents, and antioxidants**

Anesthetic agents have been shown to induce inflammation and oxidative stress in a variety of tissues [67–69,108]. In the brain, isoflurane increases expression of proinflammatory cytokines such as TNF-alpha, interleukin-1β (IL-1β), and IL-6 and a variety of anesthetics have been shown to induce ROS, reactive nitrogen species, and hydrogen peroxide formation in developing neurons [67–69,109]. Many vitamins and dietary supplements possess anti-inflammatory and antioxidant properties. Thus, it is not surprising that a number of investigations have demonstrated that certain vitamins and nutritional supplements provide some degree of protection from anesthesia-induced neurotoxicity.

For example, nicotinamide, an amide of vitamin B₃, is a potent inhibitor of proinflammatory cytokines and has been shown to prevent ethanol-induced neurodegeneration in the developing mouse brain [110]. In addition, a single 1 mg/kg dose of nicotinamide was able to inhibit ketamine-induced neuronal apoptosis in the developing brain of 7-day-old rats [111]. The protective effect of nicotinamide was associated with downregulation of Bax, which prevented cytochrome c release into cytosol and activation of caspase-3 [111].

Vitamin D₃ has also been shown to limit ketamine-induced neuronal apoptosis [112]. Pretreating rats with 20 mg/kg of vitamin D₃ 1 day prior to ketamine administration reduced the number of activated caspase-3-positive cells in the somatosensory neocortex by greater than 50% [112]. It has been proposed that the protective effect of vitamin D₃ is related in part to its effect on calcium-binding proteins and stabilization of intracellular calcium [112].

Melatonin, a hormone primarily responsible for regulating the circadian rhythm, has been shown to have antioxidant properties [113]. Investigators recently tested the hypothesis that melatonin could provide some degree of neuroprotection from anesthetics [113]. They found that escalating doses of melatonin were able to reduce the severity of anesthesia-induced neurotoxicity in the cerebral cortex and anterior thalamus in a dose-dependent manner in 7–day-old rat pups [114]. The mechanism of melatonin-mediated protection was due in part to upregulation of the anti-apoptotic protein, BCL-xL, and impaired release of cytochrome c from mitochondria [114].

L-Carnitine, an L-lysine derivative, is responsible for long-chain fatty acid transport into mitochondria for β-oxidation [115]. L-Carnitine has been shown to attenuate neurologic injury acquired with various inborn errors of metabolism and inherited mitochondrial cytopathies [115]. Its protective effect has been attributed to its ability to reduce the decay in mitochondrial function over time and preserve the membrane potential, CL content, and bioenergetic capacity of mitochondria [115]. In a recent investigation, L-carnitine significantly reduced the number of activated caspase-3-positive cells in the frontal cortex of 7-day-old rat pups exposed to 6 hours of a combination of 0.55% isoflurane and 75% nitrous oxide [115]. This protective effect was due in part to preservation of the BCL-xL/Bax ratio [115].

Another dietary supplement, omega-3 polyunsaturated fatty acids, comprises a group of essential nutrients that are important for normal brain development and function [116]. Prenatal supplementation of these important dietary nutrients was shown experimentally to provide neuroprotection in newborns exposed to hypoxic–ischemic conditions as well as hyperoxia [117,118]. Subsequently, investigators tested if omega-3 polyunsaturated fatty acid supplementation during pregnancy could protect newborn rats from anesthesia-induced neurotoxicity [116]. Dams were fed a supplemented diet from the second day of gestation until pups reached 14 days of age [116]. Prenatal dietary fatty acid supplementation reduced the number of activated caspase-3-positive cells in the cerebral cortex of sevoflurane-exposed rat pups and improved neurocognitive function compared with animals born to dams that received a non-supplemented diet [116]. Protection was suggested to be due to stimulation of anti-inflammatory and antioxidant defenses and preservation of BDNF levels in the developing brain [116].

Because anesthetics cause free radical generation, lipid peroxidation, and mitochondrial injury in many different brain regions, investigators have begun to evaluate the potential protective effect of other antioxidant agents [65]. EUK-134 is a synthetic ROS scavenger that has superoxide...


Carbon monoxide

Carbon monoxide (CO) is a colorless and odorless gas that rapidly diffuses across the alveolar capillary membrane through plasma and binds to hemoglobin when inspired [130,131]. Overt toxicity can be lethal and results from tissue hypoxia when high CO levels are encountered [132,133]. However, low concentrations of CO are known to be tissue-protective and exert anti-apoptotic properties [58,134–138]. For example, CO has been shown to prevent apoptosis in endothelium, vascular smooth muscle, liver, and lung tissue during hyperoxia, sepsis, and ischemia–reperfusion [134–138]. In recent work, investigators demonstrated that simultaneously exposing 7-day-old mice to subclinical concentrations of CO with 2% isoﬂurane prevented cytochrome c release from forebrain mitochondria and decreased the number of activated caspase-3-positive cells and apoptotic nuclei in the neocortex and hippocampus [62]. The authors identified that low concentrations of CO inhibited cytochrome c peroxidase activity in the forebrain in a dose dependent manner and suggested this mechanism to be the underlying protective effect of subclinical CO (Figure 9.1) [62]. Importantly, their findings could have translational application. This is because CO is produced endogenously as part of heme catabolism and infants and children routinely inspire low concentrations of CO when rebreathing is permitted during low-flow general anesthesia [139,140]. Thus, if anesthesia-induced neurodegeneration is demonstrated to occur in humans and the safety of subclinical CO exposure during development is established, then low-flow general endotracheal anesthesia may be developed as a standard paradigm designed to protect the developing brain of infants and children.

Hypothermia

Hypothermia has been shown to protect the developing brain from a variety of insults including hypoxic–ischemic injury [120,121]. A number of investigations have demonstrated that, even when applied shortly after such an insult, hypothermia is capable of limiting neuronal cell death [122–128]. Previous work has established that brain cooling prevents early neuronal death following injury via disruption of the excitotoxic response [129]. More recently, hypothermia has also been shown to be capable of inhibiting apoptosis in the developing brain [70]. Investigators found that reducing body temperature of 4-day-old mouse pups from 34.7°C (relative normothermia) to 29.7°C (hypothermia) reduced the number of activated caspase-3-positive neurons to levels below those seen in normothermic, non-anesthesia-exposed controls in pups exposed to either 0.75% isoﬂurane for 4 hours or 40 mg/kg of intraperitoneal ketamine [70]. Mild hypothermia (31.9°C), however, failed to provide neuroprotection from anesthesia exposure. Importantly, reducing body temperature to 29.7°C also signiﬁcantly decreased the number of apoptotic neurons in the brains of animals not exposed to an anesthetic [70]. Thus, although signiﬁcant hypothermia prevented anesthesia-induced neurodegeneration, the 5°C reduction in body temperature also inhibited natural neuronal programmed cell death [70]. Inhibition of such physiologic apoptosis could be deleterious for the developing brain and could have implications for neurodevelopment. Thus, the safety and eficacy of hypothermia must be established before it can be applied to the clinical scenario for prevention of anesthesia-induced neurotoxicity.

Xenon

Xenon is a noble gas with anesthetic properties and many attractive attributes, including low solubility with rapid induction and emergence, hemodynamic stability, and organ protection against hypoxic–ischemic insults to the heart, brain, and kidneys [141]. Xenon exerts its anesthetic effects by partial inhibition of NMDA and other glutamate receptors, and also confers organ protection by blocking excitotoxic cell death that is mediated by these receptors [142]. In neonatal rodent models, xenon also has the ability to attenuate isoflurane neurodegenerative cell death. Although conflicting with some of the rodent data, a recent study in a neonatal piglet model demonstrated that 50% inhaled xenon plus fentanyl infusion (median 50–60 μg/kg/hr) for 24 hours, at either normothermia or mild hypothermia (33.5°C), did not increase neuroapoptosis over baseline unexposed control animals, whereas 2% inspired isoflurane for 24 hours increased neuroapoptosis five- to 10-fold [142]. In neonatal rodent and piglet models of birth asphyxia, xenon plus hypothermia has been demonstrated to reduce neuronal damage; this therapy has recently been reported to be safe in a phase I human trial, and phase II human studies are currently under way [143]. All of these attributes could render xenon desirable in neonatal and infant cardiac surgery, protecting against both anesthetic-induced, and hypoxic–ischemic neuronal injury and death, further beneﬁting from the frequently utilized hypothermia techniques for neuroprotection. The limitations of clinical use of xenon include a MAC in adults of 63–71%, and a neonatal piglet MAC of 116% at normothermia which is not changed at hypothermia of
Table 9.3 Non-anesthetic preclinical experimental neuroprotective therapy approaches in animal and tissue culture models

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Neuroprotective effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Neuroprotection:</td>
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<tr>
<td></td>
<td>anesthetic-</td>
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<tr>
<td></td>
<td>induced neuroapoptosis</td>
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<tr>
<td></td>
<td>Neuroprotection:</td>
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<td></td>
<td>excitotoxic neuronal</td>
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<td></td>
<td>death hypoxia–ischemia</td>
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<tr>
<td>Erythropoietin</td>
<td>++</td>
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<td>Lithium</td>
<td>++</td>
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<tr>
<td>Hypothermia</td>
<td>+</td>
</tr>
<tr>
<td>Low-flow inhalational anesthesia/CO rebreathing</td>
<td>+++ +</td>
</tr>
<tr>
<td>Anesthetic preconditioning</td>
<td>+</td>
</tr>
<tr>
<td>Anti-inflammatory agents: nicotinamide</td>
<td>++ ND</td>
</tr>
<tr>
<td>Antioxidant agents: pramipexole, melatonin</td>
<td>++ +</td>
</tr>
<tr>
<td>Dietary supplements, vitamins: omega-3 fatty acids, L-carnitine, vitamin D₃</td>
<td>++ ++</td>
</tr>
</tbody>
</table>

33.5°C [144]. Additionally, its scarcity (0.0087 ppm in room air) necessitates special rebreathing ventilator system designs that recirculate the xenon, which have proved both complex and expensive, and to date have not resulted in commercially available devices.[141]

A summary of non-anesthetic preclinical experimental neuroprotective therapy approaches is presented in Table 9.3.

**KEY POINTS: EXPERIMENTAL THERAPY IN PRECLINICAL STUDIES**

- A number of experimental approaches have shown promise to limit or prevent anesthesia-induced neurotoxicity in animal models.
- Anesthetic preconditioning with volatile agents and dexmedetomidine utilize currently approved anesthetic drugs for neuroprotection.
- Erythropoietin, lithium, vitamins, anti-inflammatory, and antioxidant agents utilize non-anesthetic drugs for neuroprotection that are approved for use in other settings.
- Hypothermia, carbon monoxide rebreathing, and xenon are additional techniques that limit anesthetic-induced neurodegeneration in animal models.

**Future therapy**

As evidence suggesting that anesthesia-induced neurotoxicity might occur in humans continues to mount, the potential need for the practice of pediatric anesthesia to change in response may soon become incontrovertible. Although a definitive link between anesthesia exposure and neurodevelopmental impairment has yet to be established, it is important to begin to explore how pediatric anesthesiologists might adapt and evolve their management strategies to prevent or limit the potential negative impact of anesthetics on neurodevelopment. Several different experimental therapies were reviewed above that have shown promise in a variety of preclinical animal studies. Translation of such therapeutic interventions to the clinical realm might be the most reasonable and seamless first step toward changing the paradigm. In subsequent years, however, it is likely that with more extensive investigation, a number of novel agents and approaches targeting anesthesia-induced neurodegeneration will be formulated and tested. Furthermore, the possibility exists that an entirely new class of anesthetic agents, lacking the ability to trigger apoptosis in the developing brain, may be developed as a “silver bullet” solution. Thus, several different approaches and types of interventions may initially be adopted; however, with further knowledge, the paradigm is likely to change over time. With these caveats in mind, it seems prudent to think about what a reasonable neuroprotective anesthetic might look like in the immediate future, given our current understanding of the pathophysiology of anesthesia-induced neurotoxicity.

**Preconditioning**

Preconditioning may be a low-risk first step toward preventing neurotoxicity. As mentioned previously, inhaled anesthetics and ketamine have been shown to successfully precondition and protect developing neurons from anesthesia-induced apoptosis [51,94,95]. As most patients with CHD require a preoperative visit the day prior to surgery for laboratory studies, review of data, and informed consent, the opportunity exists to utilize this hospital visit for the administration of a preconditioning anesthetic agent. Treating patients with an oral premedication such as midazolam or ketamine, for example, would be very attractive due to the safety profile of these agents, the short duration of sedation, and the fact that pediatric anesthesiologists routinely administer such medications in the preoperative period, providing a comfortable familiarity. Another reasonable approach could be to administer a brief inhaled preconditioning anesthetic via facemask the day prior to surgery with an agent such as sevoflurane. Obviously, the logistics of identifying the optimal agent, determining the specific dosage and duration of exposure, defining the proper timing of administration, and establishing the ideal location and level of monitoring, and so forth would need to be determined. Furthermore, the safety and efficacy of such preconditioning must be
established in humans prior to utilizing this approach routinely in the clinical environment.

**Dexmedetomidine**

Anesthetic management of infants and young children undergoing cardiac surgery often includes a high dose opioid strategy as the foundation of the approach due to the potent analgesic properties of medications such as fentanyl and their minimal effect on hemodynamics. Over the last few years, however, fast-track anesthesia, facilitating early extubation, has gained popularity amongst pediatric cardiac anesthesiologists. Initially reserved for more straightforward cardiac surgical cases and the older child, the fast-track approach is now commonly being utilized in younger children and even in infants with single-ventricle physiology. Dexmedetomidine, due to its sedative and analgesic properties and its sparing effect on respiratory drive, has rapidly been adopted as a key component of anesthesia cocktails and successful strategies designed to enable early extubation. Importantly, fast-track anesthesia employs a low dose opioid approach. Thus, from a neurotoxicity standpoint, use of dexmedetomidine could limit and potentially obviate the need for apoptosis-inducing opioids. Because dexmedetomidine has been shown to prevent isoflurane-induced neurotoxicity in rodents, it is possible that, in the future, it could even replace opioids such as fentanyl as the mainstay of the anesthetic approach for infants and children undergoing cardiac surgery [97]. Because pediatric cardiac anesthesiologists are becoming facile with dexmedetomidine, use of such an agent as a tool to prevent or limit anesthesia-induced neurotoxicity in young children with heart disease would be quite feasible.

**Hypothermia**

Controlled hypothermia is a critical element of the management strategy of CPB and circulatory arrest in order to protect the brain and other organs from ischemia–reperfusion injury. Total body cooling to a desired temperature is routinely established following initiation of bypass. As mentioned previously, significant hypothermia has been shown to prevent anesthesia-induced neurodegeneration in rodents [70]. Because hypothermia is protective even when applied shortly after a neurologic insult, it is quite possible that our current practice during cardiac surgery may already provide adequate protection from anesthesia-induced neuronal apoptosis in the developing brain. However, this concept has never been studied in humans or in preclinical models. Obviously, if hypothermia is to be employed for the prevention of anesthesia-induced neurotoxicity in the future, the timing and degree of brain cooling necessary to prevent apoptosis will need to be investigated and potential adverse effects of therapeutic reductions in body temperature with regard neurodevelopment will need to be determined. Such an approach could be appropriate for patients undergoing open heart surgery, but how about for the general population and those undergoing closed heart surgery? It is commonly recognized that hypothermia is a potentially adverse event that can occur in infants and children following induction and during maintenance of anesthesia in the absence of using a warming device. Pediatric anesthesiologists are well aware of this phenomenon and rigorously monitor patient temperature and actively strive to maintain eutherma. However, if hypothermia is shown to prevent anesthesia-induced neurotoxicity in young children, it is possible that passive and even active cooling with an underbody water cooling blanket or other device to reduce body temperature to targeted levels could become standard. Passive cooling to induce mild-to-moderate hypothermia is commonly practiced by many pediatric cardiac anesthesiologists to provide spinal cord protection during surgical repair of coarctation of the aorta [145]. Thus, many of our colleagues are already comfortable with this approach.

**Low-flow anesthesia**

Carbon monoxide is generated endogenously via heme catabolism and is excreted via exhalation [139,140]. During low-flow anesthesia when rebreathing is permitted, infants and children are routinely exposed to CO [139,140]. Because exhaled CO is not scavenged or removed from the anesthesia breathing circuit, rebreathing exhaled CO in this context results in a subclinical CO exposure [140]. As mentioned previously, exposing newborn mice to low concentrations of CO during isoflurane exposure was shown to limit and prevent anesthesia-induced neurotoxicity [62]. Thus, it is possible that a subclinical CO exposure during an anesthetic could provide neuroprotection. If the safety and efficacy of such an exposure are demonstrated in humans, then it is possible that low-flow anesthesia could be established as a standard paradigm for infants and young children.

With regard to brain protection during open heart surgery, investigators have tested the effect of preconditioning with CO prior to CPB and circulatory arrest in piglets [146]. Preconditioning animals with 250 ppm CO for 3 hours 1 day before surgery completely protected neurons in the neocortex and hippocampus from cell death [146]. If such an approach were determined to be safe and effective for infants and children, then it is conceivable that a preconditioning anesthetic with sevoflurane, for example, could be administered 24 hours prior to scheduled open heart surgery using a low-flow anesthesia technique in order to target a specific CO exposure. Alternatively, is it possible that one day we could even be administering inhaled CO as a protective gas to our patients? After all, each pharmaceutical agent that we currently use has a toxic threshold as well as a therapeutic index. So the possibility exists that CO may have therapeutic effects at levels far below concentrations known to result in tissue hypoxia and injury. As with all of
the other approaches discussed, however, the safety and efficacy of such approaches must be established.

**KEY POINTS: FUTURE THERAPY**

- Some experimental therapies may seamlessly translate to the clinical scenario in the near future.
- Volatile anesthetic preconditioning, dexmedetomidine, hypothermia, and low-flow anesthetic techniques are already part of clinical practice and could be modified for protection against anesthetic-induced neurodegeneration.

**Directions for future research**

Future studies of anesthetic technique in CHD ideally will have prospective, randomized designs. They will also be conducted in populations that are homogeneous enough, and large enough, to have adequate power to account for confounding variables and test for clinically important differences in neurodevelopmental outcomes. One potential research strategy would be to test the hypothesis that reduction in GABA binding agent exposure, particularly VAA, would result in higher neurodevelopmental outcome scores. Larger VAA exposure was associated with lower scores in one of the cohorts reported, with a decrease of approximately one point on the BSID III cognitive score for each additional MAC-hour of exposure [91]. Because VAA dose is already subject to a large variation in practice, a design of “low-dose” vs. “high–dose” VAA could be planned. One arm of a controlled study could have minimal VAA exposure with a balanced anesthetic, and the other arm could be designed for greater VAA exposure with minimal doses of other agents. Opioid exposure was associated with slightly higher scores in one cohort [91]; variation in opioid dosing strategy could be included in the study design. Anesthetic and sedative agents that do not cause neuronal apoptosis in animal models (e.g., dexmedetomidine or clonidine) could be included in one arm of a randomized controlled trial with the aim of both reducing the doses of VAA and opioids and providing neuroprotection against VAA-induced neuronal apoptosis and hypoxia-induced excitotoxic cell death [97,147,148].

Prospective, controlled, randomized trials are generally accepted as the best study design in populations with multiple covariates. In order to minimize variation, a relatively uniform group of neonates undergoing CHD surgery should be studied, i.e. only two-ventricle complete repairs, or only HLHS patients. The HLHS patients have more exposures and thus more opportunity to create a difference in exposure level; on the other hand, they have more confounding variables and greater numbers of anesthetics. The feasibility of standardizing all anesthetics during the first months of life would be difficult. Two-ventricle patients generally have fewer confounding variables and fewer exposures, and therefore less opportunity to create differences in exposure. Whatever the study design, if a primary neurodevelopmental outcome difference of 5% (i.e., 100 vs. 95 for full-scale intelligence quotient or cognitive test of the BSID III) is assumed to be clinically significant, 400–450 evaluable subjects are required in a two-arm trial to achieve 85% power with an alpha level (type II or false-negative error) of 0.05, both generally accepted as minimum adequate standards for clinical research studies. Assuming some mortality and attrition, and accounting for interim analysis, at least 500–600 subjects would be needed for initial randomization. Such studies are complex, prolonged, and expensive, and would need to follow subjects for a minimum of 4–5 years. These studies would require participation of multiple centers, as well as significant funding of several million US dollars, necessitating involvement of government or other large funding sources. The feasibility of such studies is problematic given the current challenging research funding climate for most large funding agencies.

**KEY POINTS: DIRECTIONS FOR FUTURE RESEARCH**

- In order to fully understand the impact of the anesthetic approach on neurodevelopmental outcome in patients with CHD, rigorously designed, prospective studies will be required.
- Prospective, randomized trials with a minimum of several hundred evaluable subjects for the primary neurodevelopmental endpoint at 18–24 months will be required.
- Multicentered studies with substantial research funding are necessary to carry out these rigorous study designs.

**Conclusion**

In summary, it is now clear that commonly administered anesthetics and sedatives cause neurotoxicity in the developing mammalian brain. Although this disturbing phenomenon has not been definitively demonstrated to occur in humans, there is evidence to suggest an association between anesthetic exposure and acquired neurodevelopmental impairment in infants and children. Patients with CHD may be at greater risk than the general population due to the effects chronic hypoxemia, cerebral ischemia–reperfusion injury, and the need for repeated and prolonged exposure to anesthetic and sedative agents. With more rigorous research and better understanding, we may be able to develop novel and innovative approaches to protect this vulnerable cohort while effectively providing a quality anesthetic. Such a mission will likely define the major clinical, scholarly, and educational efforts of pediatric cardiac anesthesiologists for the next decade and beyond.
Selected references
A full reference list for this chapter is available at:
http://www.wiley.com/go/andropoulos/congenitalheart

3 Kurth CD, Priestly M, Watzman HM et al. Desflurane confers neurologic protection for deep hypothermic arrest in newborn pigs. Anesthesiology 2001; 95:959–64. This was the first study to assess the effects of anesthetics on brain injury in the context of circulatory arrest. The authors demonstrated that the volatile anesthetic, desflurane, improved histologic brain injury and neurologic outcome following deep hypothermic arrest. They conclude that desflurane may confer neuroprotection in this clinical scenario.

5 Jevotovic-Todorovic V, Hartman RE, Izumi Y et al. Early exposure to common anesthetic agents causes widespread neurodegeneration in the developing rat brain and persistent learning deficits. J Neurosci 2003; 23:876–82. This was the first study to demonstrate that administration of an “anesthesia cocktail,” consisting of midazolam, nitrous oxide, and isoflurane for 6 hours, induced widespread neuronal apoptosis in the 7-day-old rat brain.

47 Ikonomidou C, Bosch F, Miksa M, et al. Blockade of NMDA receptors and apoptotic neurodegeneration in the developing brain. Science 1999; 283:70–74. This was the first study to demonstrate that NMDA antagonism causes apoptotic cell death in the developing rodent brain.


62 Cheng Y, Levy RJ. Subclinical carbon monoxide limits apoptosis in the developing brain after isoflurane exposure. Anesth Analg 2014; 118:1284–92. In this study, the authors assessed whether low concentrations of carbon monoxide could prevent anesthesia-induced apoptosis in the developing murine brain. They found that carbon monoxide limits isoflurane-mediated neurodegeneration in a dose-dependent manner. The findings could have translational significance because infants and children routinely rebreathe exhaled endogenous carbon monoxide during low-flow anesthesia.


In this paper, investigators found that reducing body temperature of mouse pups by 5°C reduced isoflurane- or ketamine-induced neurodegeneration. However, hypothermia also inhibited natural programmed cell death in the developing brain.

73 Hofacer RD, Deng M, Ward CG, et al. Cell age-specific vulnerability of neurons to anesthetic toxicity. Ann Neurol 2013; 73:695–704. This work demonstrated that vulnerability of neurons to anesthetic exposure peaks approximately 2 weeks after cells are born. Importantly, adult-generated neurons in the olfactory bulb were also found to be susceptible to anesthesia-induced apoptosis. The findings indicate that the age of neurons dictate which cells die as opposed to the chronological age of the host.

90 Guerra GG, Robertson CM, Allon GY, et al. Neurotoxicity of sedative and analgesia drugs in young infants with congenital heart disease: 4-year follow-up. Paediatr Anaesth 2014; 24:257–65. A study of 95 infants undergoing complex cardiac surgery before 6 weeks of age, demonstrating that after multivariable adjustment, greater number of days receiving chloral hydrate as an ICU sedative was associated with lower performance IQ. They also found that larger cumulative benzodiazepine dose was associated with lower visual motor integration scores.

91 Andropoulos DB, Ahmad HB, Haq T, et al. The association between brain injury, perioperative anesthetic exposure, and twelve-month neurodevelopmental outcomes after neonatal cardiac surgery: a retrospective cohort study. Paediatr Anaesth 2014; 24:266–74. In a study of 59 infants undergoing complex neonatal cardiac surgery, an association was demonstrated between larger volatile anesthetic exposure and lower scores on the Bayley Scales of Infant Development III at age 12 months, after multivariable analysis.

97 Sanders RD, Xu J, Shu Y, et al. Dexmedetomidine attenuates isoflurane-induced neurocognitive impairment in neonatal rats. Anesthesiology 2009; 110:1077–85. In this work intraperitoneal injection of dexmedetomidine limited isoflurane-induced apoptosis in a dose-dependent manner in the hippocampus, thalamus, and cortex of 7-day-old rats exposed to 6 hours of isoflurane. Furthermore, simultaneous treatment with dexmedetomidine prevented isoflurane-induced long-term memory impairment. Thus, dexmedetomidine may provide neuroprotection from volatile anesthetic-induced injury.
CHAPTER 10

Vascular access and monitoring

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Introduction

Vascular access is an essential part of anesthetic management in children undergoing cardiac surgery. In children with congenital heart disease (CHD), particularly neonates, it may be extremely difficult to obtain secure vascular access, and thorough knowledge of pediatric vascular anatomy, as well as the skills to cannulate the vessels, is mandatory. Traditional techniques of catheter placement rely mainly on anatomic landmarks, can be time-consuming, and often involve serious risks. Higher rates of successful catheter insertion and lower rates of complications can be obtained with recently introduced ultrasound-guided techniques if properly applied during catheterization. Some complications can be life-threatening and therefore many institutions around the world recommend, and sometimes mandate, the use of ultrasound guidance to enhance patient safety, especially in cases of central venous catheter (CVC) placement. Positive outcomes and maximum benefits can only be gained if meticulous attention is paid to every aspect of catheter placement and maintenance. Hence, risk–benefit assessments should always be performed and indications considered. Large-bore peripheral venous catheters are required to administer fluids and blood products with minimal resistance to flow, arterial catheters are used for continuous blood pressure monitoring and blood sampling, and central catheters for direct infusion of vasoactive drugs and bolus administration of resuscitative drugs. Hemodynamic assessment via invasive monitoring is also crucial for understanding and responding in a timely manner to the pathophysiologic processes associated with patients’ underlying cardiac conditions and associated surgical procedures. This chapter describes techniques of vascular access for children with CHD, emphasizing ultrasound guidance for successful placement of venous...
Peripheral venous access

Peripheral venous cannulation in pediatric cardiac patients can usually be accomplished with few complications. Ideally, a large cannula is inserted into a large vein of the arm or leg, but if this is anticipated as initially difficult, another practical approach can be adopted. A small superficial vein at any site is cannulated with a small catheter (24 or 22 gauge [ga]) before induction or during inhalation induction of anesthesia. Once the airway is secured and the patient immobile, larger-bore venous access can be attempted. Cannula sizes appropriate for intraoperative use are selected according to the patient’s weight as follows: < 3 kg, 24 ga; 3–10 kg, 22 ga; 11–20 kg, 20 ga; 21–30 kg, 18 ga; > 30 kg, 16 ga. Typical locations for peripheral venous access include tributaries of the cephalic and basilic veins and dorsal metacarpal veins at the dorsum of the hands; basilic, cephalic, and median cubital veins of the forearm; the great saphenous vein at the ankle; the dorsal venous arch of the foot; and the lateral malleolus vein of the lower extremities.

Once the patient is cannulated and in the surgical position, it is important to make sure that each intravenous (IV) line is functioning without abnormal flow resistance before draping is commenced. If flow of the infused fluid in the line is in some way affected by body position (e.g., wrist flexion or extension), cautious monitoring of the catheter during surgery is necessary to avoid extravasation. Only a large-bore, short catheter in a large vein with flow unaffected by positional change should be used for rapid infusion of more viscous colloids or packed red blood cells [1]. Extravasation of these fluids can lead to compartment syndrome and the need for fasciotomy and permanent loss of limb function in severe cases.

Commonly selected locations for this purpose include the saphenous vein at the ankle, the cephalic or basilic vein of the forearm, and the external jugular vein (EJV). When the vein can be successfully punctured but advancement of the catheter to its full length is impossible, a spring-wire guidewire 0.018” (for 22 ga) or 0.015” in size may be used to facilitate cannulation [2].

Peripheral vein cannulation in pediatric patients is not always an easy task; therefore, sufficient planning and preparation often help to overcome anticipated difficulties. One of the useful tools for prediction is the difficult intravenous access (DIVA) score, which consists of four variables to which numbered scores are assigned: three points are given for prematurity; three for age less than 1 year and one point for age 1–2 years; two points for vein not palpable; and two for vein not visible. One study has shown that the first attempt at IV line placement is unsuccessful in more than 50% of children with a DIVA score of 4 or more [3]. The DIVA score has been refined and validated, and three predictors, including history of stay in the newborn intensive care unit (ICU), operator’s inexperience, and skin color, have been incorporated [4]. Recognition of a child with a high DIVA score should warn anesthesiologists and prompt them to prepare a backup plan for anticipated difficult peripheral venous access.

In the face of unanticipated DIVA, calling for the help of an experienced and skilled anesthesiologist, if available, is far more important than multiple attempts and hope for successful cannulation. Each consecutive puncture and failed cannulation increases difficulty of subsequent attempts and risk of complications.

New technologies have been developed in the past several years to facilitate venous access in children, with variable results [5–9]. Among them, ultrasound and illumination techniques are promising, particularly in children with anticipated cannulation difficulties. Ultrasound-guided methods for peripheral IV access will be discussed in detail later in this chapter. With respect to illumination techniques, a few commercially available vein locator devices can be used. The AccuVein® AV300 or AV400 (AccuVein Inc., Huntington, NY, USA) is a vein illumination device that operates by projecting infrared light, which is absorbed by hemoglobin, and making the veins visible through a viewfinder. The VeinViewer® (Luminetx Corp., Memphis, TN, USA) uses near-infrared light and projects a real-time image of the vein pattern directly onto the patient’s skin. Neither obesity [5] nor skin color [6] interferes with vein visibility. Although the efficacy and use of these devices under routine and anticipated difficult IV access conditions have not been validated in large-scale studies of pediatric patients, further evaluation would be beneficial because they are easy to operate, non-invasive, and portable.

Technique. Venipuncture is simple and common for all peripheral veins. For veins of the dorsum of the hand, holding the hand in place with the wrist fully flexed while stretching the dorsum of the hand with one’s thumb and index finger makes the dorsal metacarpal veins easier to cannulate (Figure 10.1A). If the vein is visible or palpated, the puncture is straightforward. If the vein is not visible or cannot be palpated, blind insertion attempts have traditionally been made based on typical anatomic locations. However, new devices, such as the VeinViewer®, may visualize the vessel and facilitate successful cannulation (Figure 10.1B,C). Even if blood flow is not observed in the cannula, it may be advanced into the vessel and cannulation can be confirmed by an infusion trial with a small amount of infusate. Lack of signs of local extravasation indicates successful cannulation.

Central venous access

Central venous access is often necessary during surgery for congenital heart defects to measure central venous pressure (CVP), deliver vasoactive drugs or high-osmolarity
solutions into the central circulation, and to repeatedly sample blood to monitor venous oxygen saturation and other metabolic parameters. To achieve these goals, multi-lumen catheters are recommended. The largest distal lumen should be used for pressure monitoring, whereas proximal lumen(s) should be used for other purposes including administration of vasoactive medications. Because larger-size catheters in small vessels are associated with higher rates of thrombosis, the size of the catheter should be the smallest acceptable.

In patients with single-ventricle physiology who have undergone palliative cavopulmonary anastomosis surgery, a catheter inserted via the upper limb or neck veins [10] can be used to measure pulmonary artery pressure, which may be important to assess. If access is required only for inotrope infusion, it would be prudent to insert the line elsewhere because thrombosis or occlusion of the superior vena cava (SVC) would limit pulmonary blood flow [11,12]. Catheters inserted from below the diaphragm should reach the inferior vena cava (IVC) for accurate assessment of atrial pressure [13]. In patients with single-ventricle physiology and adequate atrial septectomy, monitored pressure reflects systemic ventricular diastolic pressure. If complete atrial or ventricular mixing is observed, line flushing or bolus administration of drugs should be performed with care, because clots or inadvertent air infusion can result in paradoxical systemic embolism.

**Percutaneous central venous access**

Among various available approaches to central venous access, the percutaneous approach has become standard practice at many institutions. This has been particularly true because of the development and widespread use of portable ultrasound devices for ultrasound-guided catheter insertion (see later). Common sites for percutaneous central venous access include the internal jugular, subclavian, and femoral veins. Various central catheters are commercially available. Recommended sizes and lengths for each insertion site are listed in Table 10.1.

Full barrier precautions are mandatory upon catheter placement. Sterile technique with gowns and wide draping should be applied during all percutaneous central cannulations to reduce the risk of catheter-associated infection. After sterile skin preparation with chlorhexidine-containing solution or iodine, wide draping is performed, preferably with a clear, fluid-impermeable, adhesive and aperture drape so that the underlying anatomy is clearly visible. The Seldinger technique is the standard approach. The basic principle is to place a guidewire into the target vessel and then thread a large-bore catheter over the guidewire. For guidewire placement, either an introducer needle or an angiocatheter (catheter-over-needle) may be used. The authors’ preference is to use an angiocatheter in infants weighing less than 10 kg (see Figure 10.9). In these

**Table 10.1 Recommended central venous catheter sizes and lengths**

<table>
<thead>
<tr>
<th>Patient height (cm)</th>
<th>Internal jugular/subclavian vein</th>
<th>Femoral vein</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;60</td>
<td>20 ga, single lumen, 8 cm</td>
<td>20 ga, single lumen, 12 cm</td>
</tr>
<tr>
<td></td>
<td>3–4 Fr, double lumen, 8 cm</td>
<td>3–4 Fr, double lumen, 12 cm</td>
</tr>
<tr>
<td>60–80</td>
<td>4 Fr, double lumen, 8 cm</td>
<td>4 Fr, double lumen, 12 cm</td>
</tr>
<tr>
<td>80–130</td>
<td>4 Fr, double lumen, 12 cm</td>
<td>4 Fr, double lumen, 12–15 cm</td>
</tr>
<tr>
<td>130–160</td>
<td>5 Fr, double lumen, 12–15 cm</td>
<td>5 Fr, double lumen, 15 cm</td>
</tr>
<tr>
<td>160–170</td>
<td>7 Fr, double lumen, 15 cm</td>
<td>7 Fr, double lumen, 20 cm</td>
</tr>
<tr>
<td>&gt;170</td>
<td>8 Fr, double lumen, 16 cm</td>
<td>8 Fr, double lumen 20 cm</td>
</tr>
</tbody>
</table>
patients, a 4-Fr central catheter is routinely used. A 0.015" or 0.018" guidewire should be used for cannulation. The wire is first threaded into a 24-ga catheter to enter the vessel. Using this small, 24-ga angiocatheter to puncture the vessel may minimize hematoma formation should inadvertent artery puncture occur, and reduce damage of the vessel should the needle penetrate its posterior wall. Once the catheter is placed in the vein, a short extension tube can be attached and used as a manometer to verify venous access. This verification is extremely important in patients with cyanotic lesions, because the color of blood aspirated from the catheter is not a reliable indicator of correct venous placement. One advantage of an introducer needle is that threading the outer catheter over the inner needle is not necessary. Disadvantages include the necessity to use a large needle (20 ga for a 0.018" or 0.021" guidewire) and the possibility of damaging the guidewire if improperly inserted, which can lead to serious complications. Because the tip of the needle may damage the structure of the thin guidewire, attention should be paid not to retract the guidewire through the needle while it is still in the vessel if there is any resistance at all; they should be removed simultaneously to avoid breaking the guidewire and a fragment being retained intravascularly . Guidewires with straight, slightly curved (angled), or J-shaped tips are available. The shape of the tip may be one of the causes of unsuccessful threading [14], particularly in neonates or small infants. The radius of curvature of the wire’s J-shaped tip is often identical to or larger than the diameter of the infant’s vessel (~5 mm) [15,16]. Our preference is to use the straight end of the guidewire in this patient population (see Figure 10.9). After the desired vein is punctured, the guidewire is carefully advanced into the SVC. The resistance to the wire’s passage should be minimal; if any resistance is encountered, the wire must be carefully withdrawn. Forcing a guidewire in the presence of resistance can lead to significant complications. The electrocardiogram (ECG) should be observed carefully as the guidewire is slowly advanced. Premature atrial contractions (PACs) are usually observed as the first guidewire-induced dysrhythmias, signifying atrial location. If no PACs occur, the guidewire is most likely not in the atrium. Premature ventricular contractions, especially if multifocal in nature and occurring as the first observed dysrhythmia, indicate that the guidewire is probably in the ventricle and should be immediately withdrawn. Insertion of a transesophageal echocardiography (TEE) probe before attempting central venous access may facilitate visualization of the guidewire and confirmation of its correct location [17].

After guidewire placement, a very small incision is made followed by careful dilation and catheter cannulation. Dilators included in prepackaged CVC kits are often one size larger than the catheters (e.g., a 5-Fr dilator for a 4-Fr catheter). This might not be optimal with small infants; passage of the catheter without dilation or use of a dilator of the same size as the catheter would be preferable. This allows for the smallest possible entry into the vein, to minimize bleeding and trauma to the vessel wall, both of which can lead to thrombosis or vascular insufficiency. In small infants, attention should be paid to blood loss during the catheterization procedure; direct compression of bleeding puncture sites with the heel of the non-dominant hand should be applied while threading dilators or catheters. Difficult catheterization often requires more hands, and assistance should be requested accordingly. Once the catheter is advanced to the desired depth, it should be secured with sutures and dressing.

**Internal jugular vein**

The internal jugular vein (IJV) originates from the jugular foramen at the base of the skull. The right IJV is large and lateral to the common carotid artery (CCA) along most of its length (termed the carotid sheath) and is the most common site for central venous access in pediatric patients undergoing cardiac surgery. The IJV provides a direct route to the right atrium (RA) and is an optimal site for catheterization. In patients with supracardiac-type total anomalous pulmonary venous return (TAPVR), the vertical vein draining blood from the common chamber to the brachiocephalic vein and the left IJV and left subclavian vein (SCV) usually contains oxygen-rich blood. Oxygen-rich blood can be drawn while puncturing the left IJV, and it is sometimes difficult to distinguish whether the blood is from an artery or a vein. We recommend use of a pressure transducer for confirmation. Some surgeons discourage the use of the left veins in TAPVR. The right IJV, right SCV, or femoral veins (FVs) can be used instead of the left IJV and/or SCV.

Some simulated models have shown that penetration of the posterior wall of the IJV is unavoidable [18,19]. Inadvertent CCA puncture can occur unless its exact location is known. The CCA and IJV overlap area differs among studies from various countries and approaches [20–23]. Both the lower approach (at the junction of the two heads of the sternocleidomastoid muscle) and the higher approach (at the cricoid cartilage) provide a similar pattern of overlap (Table 10.2). The overlap between the IJV and the CCA increases with head rotation to either side [24]. In addition, the right IJV is preferred to the left because of a smaller overlap area with the CCA on the right side and its more lateral position [24]. Greater head rotation (more than 30°) to the left should be avoided, because this increases the right IJV and CCA overlap and risk of carotid puncture. Positive inspiratory pressure, but not the Trendelenburg position, can increase the cross-sectional area of the IJV [25]. Use of combination of the Trendelenburg position, liver compression, and simulated Valsalva maneuver can effectively increase the diameter of the IJV [26]. Gentle skin traction can also improve the success rate of catheterization [27]. An anchoring maneuver using a pilot needle facilitates IJV catheterization at its entry in the majority of infants. If the pilot needle is left in the IJV, and the IV catheter (22 or 24 ga) is passed just posterior to the puncture point of the pilot needle to track the pilot needle path at a 10–20°
Table 10.2 The overlapping of the right common carotid artery (CCA) and internal jugular vein (IJV) in pediatric patients

<table>
<thead>
<tr>
<th></th>
<th>CCA</th>
<th>IJV</th>
<th>CCA</th>
<th>IJV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higher approach (n = 130)</td>
<td>43.1%</td>
<td>43.8%</td>
<td>13.1%</td>
<td>11.6%</td>
</tr>
<tr>
<td>Lower approach (n = 216)</td>
<td>35.2%</td>
<td>53.2%</td>
<td>11.6%</td>
<td>11.6%</td>
</tr>
</tbody>
</table>

The CCA and IJV are at the cricoid cartilage in the higher approach and at the junction of the two heads of the sternocleidomastoid muscle in the lower approach. Schematic representation of CCA and IJV as imaged by ultrasound with operator standing at patient’s head. Results are combined from studies [19–22].

angle to the skin, a natural tumbling movement of the pilot needle helps to anchor the anterior wall of the IJV and facilitate puncture with the catheter needle [28]. The bevel-down approach to the right IJV may decrease the incidence of posterior venous wall damage and hematoma formation compared with the bevel-up approach [29].

**Technique.** With a landmark approach, the location of the clavicle, sternocleidomastoid muscle, and cricoid cartilage should be confirmed by visually observing and palpating the neck. After disinfecting the insertion site, the skin is usually punctured midway between the mastoid process and the sternal notch in the “high” approach, at the junction of the two heads of the sternocleidomastoid muscle or at the level of the cricoid cartilage in the “middle” approach, or near the jugular notch in the “low” approach (Figure 10.2). After aspiration of dark-colored blood from the punctured vessel, the Seldinger technique should be used for guidewire and catheter placement (described earlier). If the artery is inadvertently punctured, compress the puncture site for several minutes to ensure hemostasis. Ultrasound-guided puncture will be discussed in detail later in the chapter.

**Subclavian vein**

Subclavian central venous catheterization is a relatively safe procedure, with minimal complications in pediatric patients [30–34]. The SCV is an extension of the axillary vein at the outer border of the first rib, lies under the clavicle, and runs in the subclavian groove on the first rib. The SCV joins the IJV to form the brachiocephalic vein. It lies anterior to the anterior scalene muscle, and the subclavian artery lies posterior to the anterior scalene muscle. Catheterization of the SCV has several advantages, including its relatively constant position in reference to surface landmarks in patients of all ages, comfort for the awake patient, and less tip migration and greater stability with patient movement. Disadvantages include risk of pneumothorax and the potential inability to dilate the space between the clavicle and the first rib. There is also a possibility that a subclavian catheter will enter the contralateral brachiocephalic vein or ipsilateral IJV instead of the SVC.

**Technique.** For right-side subclavian venous puncture, positioning with the patient’s right upper arm abducted

0° maximizes clavicle and SCV overlap. In the 5–10° head-down tilt position, puncture the skin near the clavicle at the midpoint or just lateral to the clavicle. Advance the tip of the needle to contact the clavicle. The tip should then be advanced underneath the needle kept in the horizontal position to avoid puncturing the subclavian artery or the lung. When no blood return is obtained, withdraw the needle gently while pulling back the plug with the syringe attached to the angiocatheter. After obtaining dark-colored blood return without pulsation, cautiously advance the guidewire and then the dilator.

**External jugular vein (EJV)**

The course of the EJV can be readily seen on either side of the patient’s neck. The EJV can also be used as a peripheral vein that provides rapid and easy vascular access. Inadvertent arterial puncture is extremely rare with this approach. Although the EJV is a viable site for central
venous access with a low complication rate, the EJV has positional concerns because of its angle relative to entry to the SCV, which may hinder the passage of a guidewire into the SVC. This is particularly true in younger patients. Success rates of percutaneous central catheterization via the EJV vary from 54% to 90% [35–39].

**Technique.** With the patient’s head extended, the central portion of the EJV compressed, and the EJV stretched peripherally, puncture the skin with an angiocatheter (<10 kg, 22 ga; 10–20 kg, 20 ga; >20 kg, 18 ga) and insert a curve-tipped guidewire after obtaining dark-colored blood. A small incision with a 25- to 27-ga needle at the insertion point can aid angiocatheter insertion.

**Femoral vein**
Another major site of access to the central circulation is the FV. The FV is the most commonly accessed central route in pediatric patients outside the operating room (OR) because of the relatively high rate of success and low incidence of complications [40,41]. Once thought to be associated with an increased risk of infection, studies have since concluded that cannulation of the FV is of no greater risk than other sites [42,43]. Several studies [13] have reported that mean CVP measured in the IVC below the diaphragm is identical to that measured in the RA in patients with or without CHD (in the absence of increased intra-abdominal pressure or IVC obstruction). Agreement of IVC and RA pressures in patients with an interrupted IVC with azygos vein continuation into the SVC, commonly seen in heterotaxy syndrome, have not been evaluated; however, the catheter can be used for other purposes such as drug or fluid infusion.

**Technique.** The patient should be positioned with a rolled towel placed under the hips to obtain moderate extension. The puncture site should be 1–2 cm inferior to the inguinal ligament and 0.5–1 cm medial to the femoral artery impulse, with the needle pointed toward the umbilicus. Ultrasound guidance is useful for identifying important anatomic structures to aid in successful, uncomplicated placement (see later). It is important to puncture the vessel below the inguinal ligament to minimize the risk of retroperitoneal bleeding. Once cannulated, the Seldinger technique should be used as for IJV cannulation. The tip of the catheter should be located in the mid-IVC.

**Umbilical vein**
In neonates, a catheter can be placed in the umbilical vein for emergency access when peripheral venous access is not readily available [44,45]. This vessel can be cannulated at the umbilical stump up to a week after birth. Therefore, umbilical line placement is often performed by physicians in the neonatal ICU.

At some institutions, umbilical catheters are routinely used in neonates with cardiac disease for whom surgery is planned in the first 2 weeks of life [46]. Catheters (5-Fr double- or triple-lumen umbilical venous catheters) are used to infuse volume and vasoactive drugs as well as to concomitantly monitor CVP. One benefit of using the umbilical vein is that it spares the femoral, jugular, and subclavian veins from the risk of thrombosis and permanent occlusion. This is particularly important in neonates with specific diseases in whom multiple interventions are inevitable as they grow older. One caveat is that if the ductus venosus closes after birth, the umbilical catheter does not pass into the IVC, often ending with the catheter tip in branches of the hepatic vein. If on radiography the tip of the catheter is located at sites other than the IVC, the catheter should not be used as a central line.

**Technique.** With the sterile technique and after placing a loose tie of vessel tape around the umbilical base, the two thick-walled umbilical arteries and the single thin-walled umbilical vein can be readily identified. While dilating with a hemostat, the catheter can be passed easily without a guidewire. If resistance is minimal, the catheter can be advanced to a premeasured distance (usually 7–12 cm). Catheter tip position should be determined radiographically as early as possible to confirm its passage through the ductus venosus and into the IVC.

**Direct transthoracic intracardiac vascular access**
Intracardiac catheters are generally inserted by the surgeon under direct visualization into the right or left atrium [47,48] and secured by a purse-string suture [49]. Pulmonary artery (PA) catheters can be located high in the right ventricular outflow tract through the pulmonary valve, or in the main PA. Continuous monitoring of mixed venous saturation in the PA or SVC with an oximetric catheter can be performed with this procedure [47]. Monitoring of continuous SVC oxygen saturation has been shown to be very useful in the post-bypass management of neonates undergoing the Norwood procedure for hypoplastic left heart syndrome [50]. Intracardiac catheters are usually placed during the rewarming phase on cardiopulmonary bypass (CPB) and may be used for pressure monitoring or administration of vasoactive drugs. The benefits of this approach include less time spent on CVC placement, assurance of the location of the catheter tip, and no potential harm to the vessel. Disadvantages include unavailability of central access in the pre-bypass period and a higher risk of cardiac tamponade after catheter removal. Due to this potential risk of post-removal bleeding, mediastinal drainage tubes are usually left in place until all intracardiac lines are removed. This may also be considered a disadvantage, because removal of the lines may leave the patient without central venous access or may delay discharge from the ICU.

A left atrial catheter is often indicated if ventricular dysfunction, coronary artery perfusion abnormalities, or mitral valve dysfunction is anticipated postoperatively. Pulmonary artery catheters are particularly useful in the management of patients with preoperatively known or postoperatively anticipated pulmonary hypertension.
(e.g., obstructive TAPVR, complete atrioventricular canal, severe mitral valve disease). A PA catheter may be indicated for infants with pulmonary hypertension and patients with residual right ventricle outflow tract obstruction because pull-back of the catheter can provide a pressure gradient between the right ventricle (RV) and the PA.

**Tunneled percutaneous or intracardiac lines**

In patients with difficult venous access and an anticipated prolonged postoperative course, a tunneled silicone catheter may be used to ensure long-term central venous access. Hickman and Broviac are brands of single- and double-lumen catheters that provide external access. These catheters can be placed percutaneously in standard fashion as mentioned in the previous section, or placed transthoracically into the SVC or RA, as with a standard transthoracic catheter but with a subcutaneous tunnel separating the skin exit several centimeters from the chest wall entry site. Compared with standard polyurethane transthoracic catheters, these catheters preserve other access sites for possible future interventions and are less thrombogenic.

**Ascertaining of correct position of upper body central catheters**

Proper placement of CVCs is necessary to prevent complications and to provide accurate CVP measurements. Some experts recommend that the CVC tip should be in the SVC, above the pericardial reflection, to make sure that it is located outside the pericardium. This will minimize the risk of cardiac tamponade should perforation occur. If the CVC tip is located in the more proximal SVC, the risk of thrombosis increases, and the catheter could migrate into other vessels such as the azygos vein, where pressure monitoring will no longer represent CVP. Others recommend that the CVC tip be positioned in the SVC, just above the SVC–RA junction. This will reduce the risk of thrombosis, malposition, and tip perforation and increase the longevity of the catheter. Various methods have been proposed to determine proper placement and will be discussed below. In the OR setting, TEE-guided catheter tip positioning is a reliable and safe method and thus can be considered the gold standard [17].

**Echocardiography**

Transesophageal echocardiography is used for many congenital heart operations. Catheter tips and guidewires are easily imaged with TEE, and one study using TEE-guided CVC placement demonstrated a 100% success rate for correct placement in the SVC when TEE was used, as compared with 86% when surface anatomical landmarks were used in infants and children undergoing congenital heart surgery [17]. The TEE probe is placed before CVC attempts are made, and the SVC–RA junction in the 90° plane is imaged. When the vessel is punctured and the guidewire passed, it should be visualized passing from the SVC into the RA. Then the catheter is passed to its full length, the guidewire removed, and the tip of the CVC identified. Flushing the CVC with saline creates an easily visible stream of contrast which identifies the tip. The CVC is then pulled back until it is above the RA, in the distal SVC 1–2 cm above the crista terminalis. Using this technique, immediate, accurate confirmation of placement is obtained before final securing, and before the surgery. The proximal SVC, which is more than 2 cm above the RA, is difficult to image using TEE, so this method is most accurate in placing CVC in the distal SVC. Also, the commonly accepted radiographic SVC–RA junction is often higher than the SVC–RA junction noted by TEE [17].

Transesophageal echocardiography can also be utilized for SVC catheter placement. Park et al. reported 106 right IJV catheter placements in 2- to 12-month-old infants undergoing cardiac surgery [51]. TTE was 96.2% successful at identifying the crista terminalis and allowing placement of the CVC tip within 10 mm above this structure. A 4–10 MHz wide band linear echo probe with standard cardiac ultrasound machine was used in transverse plane at the right second, third or fourth intercostal space. Cross-sectional images of the ascending aorta, PA, and SVC were obtained, and then the probe was rotated 90° clockwise to obtain images of the SVC–RA junction. The catheter tip was advanced to the desired location, with saline flush aiding in identifying the tip. Two-thirds of the catheters could be visualized using the longitudinal view; the others could be visualized using the transverse short axis view with the catheter identified as a white dot in the SVC, and placed at the level of the PA bifurcation.

**Radiography**

The chest radiograph is still considered the gold standard to confirm proper placement of the catheter [52]; however, post-insertion chest radiography before surgical incision merely to confirm placement of the catheter tip may not be justified in the OR in terms of time, cost, and radiation exposure to the patient. A chest radiograph should be routinely obtained immediately after surgery to reconfirm catheter tip location; the catheter tip should be seen in the area from the level of the first rib to above the pericardial reflection. Based on studies on embalmed and fresh cadavers, the carina is an easily recognizable radiographic landmark in pediatric patients and can be used to confirm that the catheter tip is outside the cardiac chamber [53]. The caveat is that the commonly accepted radiographic SVC–RA junction is often higher than that noted by TEE [54]. Therefore, the catheter tip located within the atrial silhouette on the chest radiograph can be outside the atrium as documented by TEE. Furthermore, an SVC catheter directed posteriorly down the azygos vein may not be detected by anteroposterior chest radiography alone.

**Electrocardiographically guided placement**

Intravascular ECG may be used in children to guide correct CVC placement [55,56]. A normal or hyperosmolar
(3%) saline-filled lumen with a special ECG adaptor or a guidewire within the lumen attached to a sterile alligator clip serves as an exploratory electrocardiographic electrode. Prepackaged CVC sets are commercially available to allow intracardiac ECG monitoring [57]. A sudden increase in P-wave size (P atriale) occurs as the catheter enters the RA. The catheter tip can then be pulled back 1–2 cm to the desired position within the SVC. Because this method requires special equipment not always available in the OR, TEE can be used as a sufficient substitute.

**Height- and weight-based formulae**

In the absence of TEE guidance or intravascular ECG, CVC tip position may not be confirmed until postoperative chest radiography, allowing for any potential malpositioning to persist undetected. One study proposed formulae to predict the depth of CVC insertion, with the aim of preventing inadvertent catheter tip placement in the RA [58]. Using a large database of CVC placement data in children, the following formulas were developed for catheter insertion via the right IJV or SCV, with the targeted location of the catheter tip at the radiographically determined SVC–RA junction:

\[
\text{Formula (Ht/10 – 1) cm if Ht } \leq 100
\]

\[
\text{Formula (Ht/10 – 2) cm if Ht } > 100
\]

The authors also provided a weight-based formula for length of CVC insertion via the right IJV or SCV. Use of these formulae should result in CVC placement in the mid-SVC in more than 95% of patients. Caveats of these simplified formulae are that for the IJV, the puncture site is high, precisely midway between the mastoid process and the sternal notch. For the SCV, the puncture site is 1–2 cm lateral to the clavicle midpoint. The formulae must be adjusted if different puncture sites are desired. In addition, the formulae were developed for targeting of the catheter tip to the radiographic SVC–RA junction. As mentioned earlier, the radiographic SVC–RA junction is usually higher than the TEE-confirmed SVC–RA junction. A more recent study [52] used a smaller number of pediatric patients to provide height-based formulae for determining the depth of the right internal jugular catheter (Table 10.3). They used TEE or intracardiac ECG to precisely guide the catheter tip to slightly above the SVC–RA junction and measured the depth of the CVC at the site of right internal jugular catheterization. The formulas listed here have not been validated for accuracy in a prospective fashion and therefore should be used with caution.

**Peripherally (percutaneously) inserted central catheters**

Given its safety and reliability as a method to efficiently obtain central access, the peripherally inserted central catheter (PICC) has emerged as a favorable percutaneously inserted central line in pediatric patients with acute or chronic illness. The PICC line is a thin, soft, and long catheter that can be used for long-term IV antibiotics, nutrition or medications, and blood draws. In use for more than a decade [59], PICCs are routinely used in newborns expected to require prolonged venous access. The complication rate for these catheters is very low [60,61], and they are generally easy to insert into the central circulation via the antecubital, saphenous, hand, axillary, or wrist veins. Because of the increased popularity of PICCs for IV access in children, many institutions have adopted a team approach for pediatric PICC placement. Most important for successful placement is early access, before the large, visible, superficial veins are exposed to injury from attempts at peripheral IV placement. In critically ill newborns with CHD, it is best to insert a PICC line soon after hospital admission. Commercially available PICCs are 1–5 Fr, single or double lumen, 6–65 cm, and made from polyurethane or silicone. For a newborn, a 2- or 3-Fr PICC line is often used [62]. Centrally delivered medications or fluids are administered through a PICC line; however, these are often inadequate as the sole pre-bypass access for cardiac surgery. Despite the primary intention of PICCs to be placed centrally, only half are successful; however, non-centrally (mid-clavicle and more distal) placed PICCs can still be used safely and reliably for the administration of medications and isotonic fluids. Insertion of PICCs should follow the techniques described for peripheral venous access and central line insertions.

<table>
<thead>
<tr>
<th>Ht (cm)</th>
<th>IJV/SCV</th>
<th>IJV</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>3.0</td>
<td>4.5</td>
</tr>
<tr>
<td>50</td>
<td>4.0</td>
<td>5.2</td>
</tr>
<tr>
<td>60</td>
<td>5.0</td>
<td>5.9</td>
</tr>
<tr>
<td>70</td>
<td>6.0</td>
<td>6.6</td>
</tr>
<tr>
<td>80</td>
<td>7.0</td>
<td>7.3</td>
</tr>
<tr>
<td>90</td>
<td>8.0</td>
<td>8.0</td>
</tr>
<tr>
<td>100</td>
<td>8.0</td>
<td>8.7</td>
</tr>
<tr>
<td>110</td>
<td>9.0</td>
<td>9.4</td>
</tr>
<tr>
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<tr>
<td>130</td>
<td>11.0</td>
<td>10.8</td>
</tr>
<tr>
<td>140</td>
<td>12.0</td>
<td>11.5</td>
</tr>
<tr>
<td>150</td>
<td>13.0</td>
<td>–</td>
</tr>
<tr>
<td>160</td>
<td>14.0</td>
<td>–</td>
</tr>
<tr>
<td>170</td>
<td>15.0</td>
<td>–</td>
</tr>
</tbody>
</table>

Ht, height; IJV, internal jugular vein; SCV, subclavian vein.

Table 10.3 Recommended lengths for central venous catheter insertion
KEY POINTS: VENOUS ACCESS

- Obtaining venous access in infants and children undergoing surgery for CHD can be very challenging. A backup plan should be instituted in the case of anticipated or unanticipated difficult IV access.
- Selection of the catheter size and its insertion site should be tailored to patient characteristics/needs and the nature of the surgical procedure. A strategic approach is necessary to preserve access sites in small infants with single-ventricular physiology.
- For central venous access, the use of full barrier precautions and the Seldinger technique are standard practice.
- Correct position of the CVC tip is important to avoid serious complications. Various methods are available to ascertain proper placement, and understanding the advantages and disadvantages of each method is crucial.

Arterial access

Arterial catheters are necessary during congenital heart surgery to monitor beat-to-beat changes in arterial pressure and to draw intermittent blood samples. Common sites for arterial line placement include the radial, femoral, brachial, axillary, dorsalis pedis, and posterior tibial arteries. Table 10.4 displays recommended catheter sizes for arterial access based on site and patient weight. Percutaneous entry is often possible, particularly with the aid of ultrasound, but on occasion a cutdown technique may be required to expedite artery access. Ultrasound-guided insertion techniques are discussed later in this chapter.

Radial artery

This is the most commonly accessible location for initial arterial cannulation in most infants and children. Before cannulation, the Allen’s test can be considered to verify sufficient collateral ulnar circulation [63]. Cannulation ipsilateral to an existing or planned systemic-to-PA shunt should be avoided.

**Technique.** Secure the patient’s hand gently to an arm-board, with the wrist slightly dorsiflexed and with a small roll underneath it (Figure 10.3). Prepare the skin with antiseptic solution. Use palpation to identify the artery. Alternatively, audio Doppler or ultrasound guidance can be helpful if the pulse is weak. Lighter anesthesia during catheterization may provide a stronger pulse and increase the success rate. Use a 24- or 22-ga angiocatheter flushed with heparinized saline to optimize the flow of blood into the needle hub. The first attempt offers the greatest chance of success; therefore, conditions, such as lighting, positioning, and vessel identification should be optimized. Puncture of the artery is indicated by brisk flashback. Advance the needle and catheter 1–2 mm into the artery to ensure intraluminal placement and attempt to thread the catheter over the needle its full length into the artery. Alternatively, the artery can be transfixed, the needle pulled back, and the cannula gently withdrawn until brisk flashback is observed (Figure 10.3D). The cannula can then be advanced into the artery (Figure 10.3F, G) or a small 0.015″ intravascular guidewire can be inserted into the artery and the cannula advanced over the wire. Either way, minimal resistance signifies successful threading. If the first attempt is unsuccessful, additional attempts can be made at the same site or slightly proximal to it, to avoid areas of arterial spasm, thrombosis, or dissection. Circulation distal to the catheter should be determined by inspection of the color and capillary refilling time of the fingertips and nailbeds and pulse quality as determined by pulse oximetry. We recommend that the catheter be secured with clear adhesive dressing and tape, to ensure that the insertion site and catheter hub are visible.

<table>
<thead>
<tr>
<th>Weight</th>
<th>Radial/dorsalis pedis/ posterior tibial arteries</th>
<th>Brachial artery</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2 kg</td>
<td>24 ga</td>
<td>Not recommended</td>
</tr>
<tr>
<td>2–5 kg</td>
<td>22 ga</td>
<td>24 ga</td>
</tr>
<tr>
<td>5–30 kg</td>
<td>22 ga</td>
<td>22 ga</td>
</tr>
<tr>
<td>&gt;30 kg</td>
<td>20 ga</td>
<td>22 ga</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Weight</th>
<th>Femoral/axillary arteries</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10 kg</td>
<td>2.5 Fr, 5 cm</td>
</tr>
<tr>
<td>10–50 kg</td>
<td>3 Fr, 8 cm</td>
</tr>
<tr>
<td>&gt;50 kg</td>
<td>4 Fr, 12 cm</td>
</tr>
</tbody>
</table>

Femoral artery

The superficial femoral artery is large and easily accessible in most patients and is a logical choice when radial arterial access is not available. Our practice is to avoid the femoral artery for prolonged catheterization, when alternative sites are available, because of potential vascular damage of the involved leg. However, if the patient experiences extreme hypotension or peripheral vasoconstriction when no other major vessels are easily palpable, the femoral artery may represent the only viable choice for arterial catheterization. Left-sided femoral artery catheterization is preferred if future cardiac catheterization is anticipated.

**Technique.** Place a small towel under the patient’s hips to extend the leg slightly to a neutral position. Positioning can be aided by slight external rotation with the knees restrained by taping to the bed. After sterile preparation and draping, palpate the course of the superficial femoral artery and puncture the vessel 1–2 cm inferior to the inguinal ligament to avoid puncturing the artery above
the pelvic brim, where a retroperitoneal hematoma could form. Audio Doppler or ultrasound can be used to identify the course of the vessel if the pulse is weak. Various puncture techniques are available: direct puncture with an angiocatheter; an introducer needle supplied with a commercially prepackaged kit; or a 21 ga butterfly needle with the extension tube removed. The needles should be flushed with heparinized saline to increase flashback. Use a small, flexible, 0.015” or 0.018” guidewire. Threading a polyethylene catheter over the guidewire can often be done without making a skin incision. Importantly, a dilator should not be used because it could cause arterial spasm, dissection, or bleeding if the puncture site is large. Secure the catheter by suturing around the entry site and suturing wings around the hub. Distal perfusion should be assessed immediately, and a pulse oximetry probe should be placed on the foot for continuous monitoring and early warning of poor arterial perfusion.

**Brachial artery**

The brachial artery has been used successfully as an arterial access site in neonates and small children [64]. However, this site may have theoretical concerns because it has poor collateral circulation compared with the radial, femoral, and axillary arteries, though this has not been proved by any studies to date. The present consensus is that the brachial artery should be reserved for situations when other options are limited, for example, when a right upper-extremity arterial line is necessary to monitor pressure during cross-clamping for repair of coarctation of the aorta, CPB for aortic arch hypoplasia, or interruption.
Technique. A 24-ga catheter should be used in patients weighing less than 5 kg. Restrain the arm in a neutral position on an armboard, and identify the arterial pulse above the elbow crease, above the bifurcation into the radial and ulnar arteries. The method of cannulation is the same as for radial arterial catheterization. Again, distal perfusion should be monitored continuously by pulse oximetry. The catheter should be replaced postoperatively with a catheter at a site that has better collateral circulation as soon as possible.

Axillary artery
The axillary artery is large and well collateralized. Several studies have shown this artery to be a viable option for critically ill children when other sites are not accessible [65–67]. In addition, the complication rate is low. However, given the potential for arm and hand ischemia and intrathoracic bleeding, the axillary artery should be a site of last resort when other options are not available.

Technique. Abduct the arm 90° and extend it slightly at the shoulder. Palpate the artery high in the axilla, puncture with an angiocatheter, and exchange over a guidewire for a longer catheter. A short catheter may be pulled out of the vessel with shoulder extension. Therefore, longer catheters (e.g., 5 cm) are recommended. As with the brachial artery, distal perfusion should be assessed and carefully monitored for potential upper-extremity ischemia. Catheter tip position located outside the first rib should also be confirmed by chest radiography. Because the axillary artery is close to the brachiocephalic artery, it is imperative to flush the catheter gently by hand after blood draws, thereby preventing air bubbles or clots from being introduced into the circulation and minimizing the risk of retrograde cerebral embolization.

Umbilical artery
The umbilical artery can be cannulated in a newborn during the first 72 hours of life and is the site of choice in newborns requiring surgery within a week after birth. Umbilical artery catheterization entails potential risks regardless of the position of the catheter; placement of the catheter with its tip at the seventh to eighth thoracic segment may be associated with fewer complications than placement at lower positions [68,69]. Umbilical arterial lines have an uncertain link with necrotizing enterocolitis. A neonate with ductus-dependent circulation, low diastolic pressure, and subsequent systemic steal can be at increased risk of this complication. Umbilical catheters are generally inserted in the delivery room or in the neonatal ICU shortly after birth. Lower-extremity emboli, vascular insufficiency, and renal artery thrombosis have been reported with this site; however, the overall risk is low, and the site is highly desirable because it is a large central artery, which allows for accurate pressure monitoring throughout surgery, while preserving other sites for potential future arterial access.

Technique. Prepare the umbilical stump in a sterile manner and transect. Two small muscular-walled arteries and a larger thin-walled vein are easily identified on the umbilical cord cutoff. Insert a 3.5 Fr catheter blindly into the artery after dilating the vessel. The catheter tip should be placed at the level of the diaaphragm or low in the descending aorta, and its position should be confirmed radiographically as soon as possible.

Temporal artery
The superficial temporal artery was widely used, particularly in premature babies. However, it is now avoided because of potentially severe cerebral thromboembolic complications [70,71]. The exception is when brachiocephalic pressure must be measured during surgery for an aberrant subclavian artery (e.g., corrections for coarctation of the aorta, aortic arch interruption or hypoplasia with an aberrant right subclavian artery arising distal to the obstruction); the only way to measure pressure during cross-clamping or bypass is via direct aortic pressure. This site should be used only during surgery, and the catheter must be removed immediately after operation.

Technique. Use a 24 ga catheter for newborns. Palpate the artery just anterosuperior to the tragus of the ear, just superior to the zygomatic arch. The artery should be approached with a very superficial approach angle (e.g., 10–15°). Cannulation is performed in the same manner as with the radial artery.

Dorsalis pedis/posterior tibial arteries
Peripheral vasoconstriction and vasomotor instability during the early post-CPB period makes the superficial arteries in the lower extremities less suitable as sites for arterial cannulation than the radial artery. An accurate arterial pressure waveform cannot be obtained during the early post-bypass period. These arteries may be indicated for non-bypass surgeries or for continuous pressure monitoring in the ICU.

Technique. For the dorsalis pedis artery, position the foot in slight plantar flexion to straighten the course of the artery, which can be palpated between the second and third metatarsals. For the posterior tibial artery, dorsiflex the foot to expose the artery between the medial malleolus and Achilles tendon. The artery is often deep to the puncture site and may require a steeper puncture angle. Fix the patient’s ankle with the arterial line to a board (Figure 10.4) so that the line is not accidentally removed as it is covered by surgical drapes.

Ulnar artery
The ulnar artery is only considered when attempts with the radial artery have been unsuccessful or the vessel has thrombosed due to past interventions. It should be used as the last resort, when other options are not available. There
is a high risk of ischemia of the hand if both radial and ulnar artery perfusions are severely compromised. However, one study of 18 ulnar artery catheters in a pediatric ICU reported an ischemia rate of 5.6%, no different from those associated with radial and femoral artery catheters [72].

**Arterial cutdown**

Cutdown of the radial artery is a reliable and efficient method for establishing arterial access during congenital heart surgery. This method is used as the first and primary method of securing arterial access in some institutions, whereas others only resort to it when all other attempts fail. Despite the speed and ease of access for cutdown, the existing literature indicates that a percutaneous approach is favorable to cutdown in terms of complications (e.g., bleeding, infection, failure, distal ischemia, long-term vessel occlusion).

**Technique.** Position the arm as for percutaneous radial catheterization. After preparation and draping for surgery, make an incision at the proximal wrist crease, between the styloid process and the flexor carpi radialis tendon. Isolate the exposed artery with a heavy silk suture, vessel loop, or right-angle forceps. It is no longer considered necessary to ligate the artery distally to prevent bleeding; the artery can remain patent after cutdown if not distally ligated. The simplest technique is to directly cannulate the exposed artery with an angiocatheter, in the same manner as for placement of a percutaneous radial artery catheter. Suture the catheter to the skin at its hub, and close the incision with nylon sutures on either side of the catheter. To remove, cut the suture at the hub of the catheter, remove the catheter, and apply pressure for a few minutes until bleeding stops. The remaining skin sutures can be removed later.

**KEY POINTS: ARTERIAL ACCESS**

- In most cases of congenital heart surgery, the radial artery is the preferred site for arterial pressure monitoring, with the second choice being the femoral artery.
- Like venous access, a strategic approach is necessary for selecting the site of arterial access for univentricular patients.
- With a few exceptions, temporal artery cannulation should be avoided because of the risk of devastating cerebroembolic complications.
- Despite theoretical concerns, brachial artery cannulation has been successfully performed in neonates and infants and may be a candidate cannulation site after failure of radial artery catheterization.

**Ultrasound guidance for vascular access in congenital heart surgery**

Ultrasound-guided vascular access can increase the success rate of line insertion and decrease complication rates associated with catheterization. Ultrasound guidance has been used in many institutions to enhance patient safety, especially during central venous line placement. Understanding the anatomic relations of tissues on sonographically obtained images is essential for safe catheter placement. Fundamental knowledge of the physical principles of ultrasound waves and equipment is necessary for understanding the sonoanatomy of the visualized tissues. Various studies have reported increased success rates and safety of vascular access with the ultrasound guidance.
Sonoanatomy
The differentiation of veins from arteries or muscle can be accomplished with ultrasonography, and it also allows detection of peripheral veins in children. Muscles are moderately echogenic, and adipose tissue is relatively hyperechoic compared with the inner side of a vein filled with low blood echogenicity. Veins are easily compressed, and their lumens are not visible when under compression; thus, they are usually distinguished from muscle or adipose tissue by visual contrast of echogenicity. Another method is to use a low-velocity color Doppler signal (5–20 cm/s), which can be observed as intraluminal color flow. All three layers of a vein wall cannot be distinguished on ultrasonographic images. When the vein is in spasm, the inner layer of the smooth muscle becomes thicker and more visible.

For pediatric vascular access, a linear probe with 5- to 15-MHz frequency and 1–5 cm depth settings is ideal and adequate in most cases. Higher-frequency ultrasound with 50 MHz can visualize more superficial structures [73]. Various types of portable linear probes are commercially available. Portable ultrasound machines equipped with linear probes are more favorable for pediatric central vein access than larger multifunctional ultrasound imaging systems equipped with TEE probes due to limited space in the OR. A hockey stick-type, 30-mm-wide, small probe might be optimal for vessel imaging, especially in neonates and infants; however, it is sometimes difficult to hold such small probes stably on the tiny necks of neonates and infants. The beveled needle tip produces two echoes, which are obtained when the needle tip reaches the vessel lumen [74]. The distal echo is more intense than the proximal one. The echogenic polymer-coated needle is better visualized than Teflon-coated, etched-tip, echogenic polymer-coated, or untreated needles [75].

Ultrasound-guided peripheral vein access
Ultrasound guidance can improve the success rate of peripheral venous access in children with difficult venous access compared with the blind technique [76] and is a promising method. Ultrasound-assisted catheterization saves time spent in the OR when a difficult access scenario is encountered and can, in fact, circumvent this very scenario when chosen as a primary method after adequate patient evaluation.

Technique. The basilic vein is suitable for ultrasound-guided peripheral venous puncture because it runs on the convex portion of the forearm. It is relatively easy to visualize the basilic vein directly and ultrasonographically, especially in lean patients. Search for a long straight portion of the basilic vein. Place the ultrasound probe at an angle of 60–80° angle to the skin. For the ultrasound-guided, short-axis, out-of-plane technique, sweep or swing the probe along the arm and place it perpendicular to the vein. The vein should be kept continuously in the middle of the visualized field without moving the probe to the side in the perpendicular position. Puncture the skin and visualize the tip of the needle at the center of the anterior wall of the basilic vein. The probe can be moved along the vein while maintaining the probe position perpendicular to the vein. Penetrate the anterior wall with the inner needle of the angiocatheter at an angle of 5–10° to the skin. Carefully advance the needle, paying attention not to penetrate the posterior wall of the basilic vein. Two high-echoic enhancements from the needle tip placed inside the vessel are observed in the out-of-plane image. After obtaining venous blood return from the inner needle, an approximate 2-mm advancement of a 24 ga angiocatheter is required to penetrate the anterior wall by the outer catheter of the angiocatheter. Penetration of the inner needle and outer catheter beyond the anterior wall of the basilic vein is more visible in plane than out of plane. Blood pressure cuff inflation can increase the lumen of the basilic vein in adults and potentially in children.

Ultrasound-guided central vascular access
Ultrasound-guided central vascular access has become routine in many institutions, although superiority of either the real-time ultrasound-guided approach or the anatomic landmark approach for locating the IJV has been a matter of debate. The use of ultrasound guidance has been questioned for central catheterization in children; however, many researchers support its application [77–80]. Ultrasound is particularly useful for assisting access to the IJV and FVs in all age groups and the SCV in infants. Randomized studies [78, 81–86] have shown that arterial puncture rates during central catheterization are higher with landmark than with ultrasound guidance (Table 10.5). The use of real-time ultrasound increases insertion success, has higher overall success, reduces access time, and reduces arterial puncture; however, ultrasound-assisted central vein catheterization is not totally reliable. A video analysis reported accidental artery catheterization in five CCAs and one femoral artery despite the use of real-time ultrasonographic guidance.

<table>
<thead>
<tr>
<th>Author</th>
<th>Arterial puncture (n)/attempts (%)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Ultrasound</td>
</tr>
<tr>
<td>Verghese et al.</td>
<td>0/43</td>
</tr>
<tr>
<td>Grebenik et al.</td>
<td>7/59</td>
</tr>
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<tr>
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<tr>
<td>Chuan et al.</td>
<td>1/32</td>
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<tr>
<td>Froehlich et al.</td>
<td>10/119</td>
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<td>Bruzoni et al.</td>
<td>3/66</td>
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<tr>
<td>Total</td>
<td>23/405 (5.7%)</td>
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The inadvertent arterial puncture rate is lower with ultrasound guidance than with the landmark method (P = 0.0026).
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probably due to penetration of the posterior wall of the IJV [87]. Simulated models have indicated that penetration of the posterior wall of the IJV is unavoidable in certain cases [18,19]. The available evidence tends to support the use of two-dimensional ultrasound to augment the landmark technique for pediatric catheter placement, but more studies are needed [79,85,86,88]. The use of ultrasound during central catheter placement in adults and children remains limited, not universally adhered to, and is most strongly associated with the availability of equipment. Trained anesthesiologists can insert IJV lines safely using the landmark technique [88], and ultrasound-guided insertion techniques require education, training, and practice even when working with the adult patient population. Despite the widespread use of ultrasound in children, formal training for this technique is typically lacking. Trainees may benefit more than experienced operators from the use of ultrasound for central catheterization [89,90].

Ultrasound-guided IJV puncture

The IJV is frequently used for ultrasound-guided or ultrasound-assisted vascular access in children. (Figure 10.5) Ultrasound can be used to place central catheters in the IJV even in neonates and infants. Ultrasonographic localization of the IJV is likely superior to the landmark technique in terms of overall success, speed, and decreased incidence of carotid artery puncture [81]. Both audio Doppler and ultrasound are useful for access to the IJV in children older than 1 year of age [83]. Ultrasound may be more useful than audio Doppler in infants and neonates. Location of the IJV with static ultrasonography and the anatomic landmark approach or combining pre-procedural ultrasonographic assessment with real-time ultrasound-guided venipuncture is recommended for central vein catheterization [77,91,92].

In pediatric patients, anatomic structures of the vertebral, thyrocervical trunk, suprascapular, transverse cervical, and inferior thyroid arteries, as well as the CCA, can be observed by ultrasonography including Doppler color flow imaging (Figure 10.6). The brachiocephalic artery divides into the right subclavian artery and the right CCA. The right vertebral artery branches from the subclavian artery. The thyrocervical trunk bifurcates from the subclavian artery next to the vertebral artery and into mainly three arteries, the suprascapular, transverse cervical, and inferior thyroid arteries. Numerous variations have been reported for the vessels arising from the aortic arch [93], with different origin variants of the right vertebral artery and some variants of the thyrocervical trunk and its branches [94]. The vertebral artery usually lies under the CCA and enters the vertebral column at the fifth or sixth vertebra; however, it sometimes lies under the IJV. The relationships between the IJV and the vertebral artery can be seen in out-of-plane images (Figure 10.6A) and in-plane images (Figure 10.6 B) with Doppler color flow ultrasound, even in neonates and infants. The depth from the skin to the vertebral arteries, the width of the vertebral arteries, and the distance from the IJVs to the vertebral arteries (Figure 10.7), as well as the extent of overlap between the IJVs and vertebral arteries, with scores of 0 to 3 for each measurement, should be checked [95]. The summed scores are categorized as low risk (0–3), moderate risk (4–7), or high risk (8–10). High risk is approximately 13% for accidental puncture of the vertebral arteries. From the thyrocervical trunk (Figure 10.8A), the suprascapular, transverse cervical (Figure 10.8B), and inferior thyroid arteries arise, in that order. Inexperienced practitioners can mistake these arteries for the vertebral artery with ultrasound imaging of this vessel [96]. In some cases, such as anomalous origin of the vertebral artery or IJV spasm, the relationship between the vertebral artery and the IJV may be more clearly understood with in-plane imaging [97].

Technique. For right-side IJV puncture, the ultrasound instrument may be placed on the right side of the patient. Before catheterization of the IJV, the pulsation of the carotid artery should be confirmed by palpation at the middle of the patient’s neck. (Figure 10.9A2). Under the IJV, the pulsatile vessel, possibly the vertebral artery, can sometimes be felt to be obviously different from the carotid artery. The relationship between the vertebral artery and the IJV, in addition to the relationship between the carotid artery and the IJV, should be assessed by ultrasound imaging out of plane (Figure 10.9B1) and in plane (Figure 10.9B2). Images of other arteries around the IJV, such as the subclavian artery, thyrocervical trunk (Figure

![Figure 10.5](image_url) Schematic of the anatomic relations among the common carotid artery (CCA), internal jugular vein (IJV), vertebral artery (VA), thyrocervical trunk (TCT), subclavian artery (SCA), subclavian vein (SCV), suprascapular artery (SSA), transverse cervical artery (TCA), and inferior thyroid artery (ITA).
Figure 10.6 Out-of-plane (A) and in-plane (B) Doppler color flow imaging of the common carotid artery (CCA), internal jugular vein (IJV), and vertebral artery (VA) in a 5-month-old infant.

Figure 10.7 Schematic representation of risk classification for vertebral artery puncture. The width, depth from the skin, the distance from the IJV of the VA, and the overlapping between the IJV and VA are illustrated using out-of-plane Doppler color flow imaging. In high-risk cases, the vertebral artery (VA) is wide (>4 mm), locates shallow (<15 mm from the skin), near the internal jugular vein (IJV) (<2 mm), and overlaps with the IJV. In low-risk cases, the VA is small (<2 mm), locates deep (>20 mm from the skin), distant from the IJV (>6 mm), and does not overlap with the IJV. The common carotid artery (CCA) does not affect the classification.

10.8A), transverse cervical artery (Figure 10.8B), and inferior thyroid artery, are sometimes obtained. After disinfecting the puncture site, place the probe with sterilized cover perpendicular to the IJV using the swing or sweep technique to keep the probe perpendicular to the vein in the ultrasound-guided, out-of-plane technique. Before puncturing the skin under real-time ultrasound guidance, depress the targeted skin surface puncture point above the IJV with the tip of a dull, metal, sterilized instrument, such as a hemostat, to simulate puncture without puncturing the skin surface. Obtain an ultrasound image of the intended needle on the screen to confirm the accurate point of puncture at the midpoint between the outer and inner wedges of the IJV. The IJV should be continuously kept in the middle of the monitor without moving the probe to the side and maintaining its perpendicular position. The tip of a 24 ga angiocatheter may be placed at a precalculated angle to the skin (Figure 10.10). Puncture the skin and visualize the tip of the needle at the center of the anterior wall of the IJV. The probe can be moved along the IJV, maintaining it perpendicular to the vein. Bear in mind that the probe is 12–16 mm thick in its short axis, which hinders the proper advancement of the needle. By inserting the needle 3–5 mm below the skin and then placing the probe near the needle, one can avoid hindrance by the probe – considering the relationship between the
depth from the skin and the angle of the probe. Continue observing the tip of the needle on ultrasound throughout the procedure. The tip can be observed at the anterior wall of the IJV (Figure 10.9C1). Two bright echo enhancements of the tip may be seen inside the IJV (Figure 10.9C2). Additional needle advancement is necessary to penetrate the anterior wall with the outer catheter. The distance from the tip of the inner needle and the tip of the outer catheter is approximately 2 mm for a 24 ga angiocatheter. After obtaining dark-colored non-pulsatile blood return (Figure 10.9D1), the slightly curved guidewire should be carefully inserted into the IJV (Figure 10.9D2). When any resistance is encountered during guidewire advancement, advancement must be stopped, and the blood return should be reconfirmed. The course of the guidewire should be confirmed by ultrasound (Figure 10.10) or fluoroscopic imaging before inserting dilators. If there is no blood return, the needle should be withdrawn, and re-puncture is required. If inadvertent artery puncture occurs, press on the puncture site for several minutes to aid in hemostasis. After smooth insertion of the guidewire, the outer catheter must be advanced carefully into the IJV (Figure 10.9D3), and dark-colored blood return should be reconfirmed (Figure 10.9D4) to avoid artery catheterization. As discussed earlier, once the catheter is placed in the vein, a short extension tube can be connected to the catheter, which can then be used to verify venous access. Carefully insert the dilator along the guidewire so as not to damage vessels or the guidewire while confirming the smooth movement of the guidewire. If any resistance is felt during dilator insertion, stop the advancement and confirm the smooth movement of the guidewire in the IJV. Use fluoroscopy if necessary. Guidewire deformation may suggest complications such as vein or artery perforation. Confirmation of an in-plane, long-axis image of the guidewire (Figure 10.11) is useful in most patients [98]. Careful insertion of dilators is mandatory to avoid serious complications.

Ultrasound-guided SCV puncture

Central catheters can be placed via the SCV under ultrasound guidance [80, 99–101]. The SCV, in addition to the IJV, carotid artery, clavicle, and its shadow can be identified by transectional scanning (Figure 10.12). An ultrasound-guided supraclavicular approach for SCV puncture is now possible for central venous catheterization in small infants, offering all of the advantages of SCV catheterization without the risk of “pinch-off” syndrome [99]. Supraclavicular ultrasound-guided catheterization of the SCV in the pediatric and neonatal ICU appears to be a promising technique in the emergency context [100]. It is safe and reliable, with few early complications. Furthermore, owing to the low level of sedation needed for its placement, it does not compromise the airway of the patient.

Technique. The principle of the ultrasound-guided approach for SCV catheterization is to place the ultrasound probe at the supraclavicular level to obtain a longitudinal view of the SCV and to gain access to the vein via the usual infraclavicular route for cannulation. Place the ultrasound probe on the mid-portion of the neck. Slide the probe caudally, and lean 45–60° to the skin. Both the subclavian artery and vein are first visualized transversely under the IJV, and then a longitudinal view of the brachiocephalic vein, beginning at the junction of the IJV–SCV, can be obtained. After reaching the IJV–SCV junction, rotate the ultrasound probe laterally and caudally to obtain longitudinal images of the SCV and the brachiocephalic vein. With in-plane imaging, place the needle under the probe to simultaneously observe the SCV and the needle tip. Puncture the mid-portion of the venous anterior wall. After obtaining dark-colored venous blood, insert the guidewire, and advance the procedure as for ultrasound-guided IJV catheterization.

Figure 10.8 Out-of-plane Doppler color-flow imaging of the neck vessels. (A) Out-of-plane Doppler color-flow imaging of the common carotid artery (CCA), internal jugular vein (IJV), subclavian artery (SCA), thyrocervical trunk (TCT), and subclavian vein (SCV) in a 5-month-old infant. The image was obtained near the clavicle. (B) Imaging of the CCA, IJV, and transverse cervical artery (TCA) in an 11-month-old infant. The image was obtained at a site slightly caudal from the mid-portion of the neck, above the clavicle.
Figure 10.9 Internal jugular vein (IJV) puncture under real-time ultrasound guidance. The distance from the clavicle and the angle of the mandible is approximately 60 mm (A1). The common carotid artery (CCA) and the IJV are outlined and palpated (A2). The CCA and the IJV are visualized by ultrasound Doppler color flow out-of-plane (B1) and in-plane (B2) (VA, vertebral artery). The tip of the angiocatheter is advanced into the IJV and positioned at the anterior wall of the IJV (C1). Two bright echo enhancements are seen at the tip of the needle (C2). Blood return is obtained through the 24 ga angiocatheter; dark-colored and non-pulsatile blood return is obtained (D1). Blood return has increased (D2). The guidewire is inserted and the needle is advanced (D3). We always suspect that the guidewire might possibly advance into arteries behind the IJV. Dark-colored blood return is obtained again; this blood is believed to be venous (D4).
Figure 10.10 The relationship between ultrasound beam and needle angles. To effectively obtain an image of the needle tip on the monitor, the ultrasound beam and needle angles should be as parallel to each other as possible. More than an 8-mm distance between the center of the needle and the puncture site on the skin surface is required when a 16-mm-thick ultrasound probe is used. When the internal jugular vein (IJV) with a 7-mm anterior-posterior length is located 7 mm beneath the skin, the optimal beam angle is 70–80° to obtain a good image of the needle tip in the IJV while advancing the needle at a 45° angle to the skin. When the beam angle is 60° to the skin, the optimal angle of the needle is approximately 30° angle to the skin. Adjust the angle according to the probe thickness and IJV depth.

Figure 10.11 In-plane ultrasound images of the guidewire (GW) in a 6-month-old infant. (A) The GW is seen in the internal jugular vein (IJV). (B) The IJV is compressed, and the inner portion of the IJV cannot be seen.

**Ultrasound-guided brachiocephalic vein puncture**

Ultrasound-guided supraclavicular catheterization of the brachiocephalic vein is now possible for central venous line placement in small children. Place the broadband linear array ultrasound probe in the supraclavicular region to obtain a longitudinal view of the brachiocephalic vein, beginning at the junction of the IJV and SCV. Using the in-plane technique, direct the needle under ultrasound guidance into the brachiocephalic vein. This provides good needle guidance with no disturbing ultrasound shadow caused by bony structures. The success rate of central catheterization via the brachiocephalic vein in children appears to be very high [102].
Ultrasound-guided EJV puncture
The EJV can often be seen on the lateral side of the patient’s neck. Ultrasound imaging facilitates confirmation of its course; however, safety and success rates of the conventional surface anatomic landmark technique and the ultrasound-guided technique are similar for inexperienced trainees [103].

Ultrasound-guided FV puncture
The FV is an optimal site for ultrasound guidance, and the infection rate does not appear to be high, as mentioned earlier.

Technique. As described earlier, the patient is positioned with a rolled towel under the hips for moderate extension. For right-side FV puncture, place the ultrasound monitor on the patient’s left side. The practitioner may stand on the patient’s right side in order to see the monitor over the patient. Check to ensure that the femoral artery and FV are 1–2 cm from the inguinal ligament by palpation, and then use the ultrasound. The femoral artery is located on the left, lateral side and runs toward the practitioner with a pulsatile, Doppler red-colored flow. The FV is located on the right medial side and runs away from the practitioner with a non-pulsatile, blue-colored flow. Before insertion, check the course of the vessels, and place the probe perpendicular to the FV using the swing or sweep technique. The FV in children is located 7–22 mm from the skin [104], which is usually deeper than the IJV and enables one to obtain an ultrasound image more easily than for the IJV. After sterilization, puncture the skin 1–2 cm from the inguinal ligament according to the probe thickness as described for ultrasound-guided IJV puncture.

Ultrasound-guided saphenous vein puncture
Ultrasound facilitates venous puncture of the great saphenous vein. Direct visualization via ultrasound is a promising technique for the establishment of venous access of the great saphenous vein at the level of the medial malleolus in infants [105].

Ultrasound-guided arterial catheterization
Ultrasound-guided radial artery catheterization can be useful even in neonates and infants. Radial artery insertion by ultrasound is often selected after the failure of radial artery catheterization by palpation. Ultrasound can visualize the course of the small radial artery even in difficult cases in neonates and infants. Highly successful catheterization can often be achieved when ultrasound images of the tip of the puncture needle and the radial artery are obtained in the same screen under the skin. Ultrasound guidance can improve the success rate of artery catheterization in infants. Fewer attempts with the ultrasound technique are required compared with the traditional technique [106,107]. Ultrasound-guided radial artery catheterization in infants and small children can provide a greater chance of success at the first attempt compared with the Doppler-assisted technique [108]. Serious complications, such as permanent ischemic damage, are infrequently observed with ultrasound-guided arterial catheterization for perioperative and intensive care monitoring. However, ultrasound guidance may not facilitate faster catheterization of the radial artery in children.

Technique. Prepare the patient’s hand position as described for the palpation method (see earlier). Before catheterization of the radial artery, the course of the radial artery can be palpated and then confirmed with ultrasound Doppler color flow. Once the radial artery has been located by ultrasound, the pulsation of the radial artery becomes easier to capture visually on the monitor, even in neonates and infants. After disinfecting the skin, place the probe with sterilized cover directed perpendicular to the radial artery using the swing or sweep technique to keep the probe directed perpendicular to the artery using the ultrasound-guided, out-of-plane technique. Obtain the ultrasound image of the intended needle on the screen to confirm the accurate point for puncture. The radial artery image should be continuously maintained in the middle of the monitor. When bright-colored, brisk flashback is obtained from the inner needle while puncturing, advance the catheter 1–2 mm to enter the artery. When the artery is transfixed, withdraw the needle and gently withdraw the catheter until brisk flashback is observed. The catheter can then be advanced into the artery. Connect the catheter to the pressure tubing, paying close attention to avoiding air in the line. Place a cushion between the skin and the catheter with the connector to avoid skin necrosis, and cover the catheter with the connector with sterile tape. We often obtain non-pulsatile, bright-colored blood from a 24 ga angiocatheter just after catheterization. Pulsatile blood inside the connected needle can be obtained after connecting to the pressure monitor line.
Percutaneous PA catheterization

Although multi-lumen, flow-directed PA catheters have been used widely in adult practice, great controversy has arisen during the past decade [109–113], and their use has decreased significantly, especially in children, and become rare in infants [114]. The Pulmonary Artery Catheter Consensus Conference published a consensus statement regarding the use of PA catheters in pediatric patients [115]. It recommends that PA catheters should only be used in selected patients, such as those with pulmonary hypertension and shock refractory to standard fluid resuscitation and vasoactive agents [116]. In patients undergoing congenital heart surgery, PA pressure monitoring may be indicated for reasons related to the cardiac condition of the patient or the nature of surgery. Patients undergoing surgery on left-sided lesions and who do not have intracardiac shunting, those who are at risk of left ventricular dysfunction, and those with pulmonary hypertension may need PA catheterization. Examples of surgical procedures include aortic surgery, aortic valve surgery or replacement, subaortic resection or myomectomy for hypertrophic cardiomyopathy, and mitral valve repair or replacement. However, PA catheterization has a limited role, if inserted percutaneously, for several reasons. First, adequately sized catheters and sheaths are not available in sizes small enough for the smallest pediatric patients. Secondly, most of these patients have intracardiac shunting, and standard thermodilution cardiac output (CO) measurements, and mixed venous oxygen saturation (SvO₂) measurements are unreliable. In addition, a PA catheter in the right side of the heart may interfere with the surgical field. Thus, when PA pressure or SvO₂ monitoring is indicated, transthoracic PA lines placed under direct visualization at the end of CPB surgery are the most commonly used approach.

Percutaneous PA catheterization is used less frequently in children than in adults, mainly due to greater difficulty in gaining access because of patient size and the unavailability of small-sized PA catheters; however, if the patient is large enough to insert a 5 or 6 Fr introducer sheath in the FV or IJV, percutaneous PA catheter insertion may be feasible. Pulmonary artery catheters are available in various sizes (4–8 Fr) for different functions, such as pressure monitoring, thermodilution measurement of intermittent or continuous CO, continuous measurement of venous saturation, and cardiac pacing. Commonly used sizes for pediatric patients are 4 Fr (non-balloon-tipped, two-lumen, oximetry catheter), 5 Fr (balloon-tipped, four-lumen, thermodilution catheter), 5.5 Fr (balloon-tipped, four-lumen, oximetry and thermodilution catheter), and 7.5 and 8 Fr (balloon-tipped, three-lumen, oximetry and thermodilution catheter).

It must be stressed that a PA catheter should be used as a diagnostic and hemodynamic monitoring tool and not as a therapeutic intervention; interpretation of the data derived from a PA catheter and subsequent management decisions are crucial to benefit patients fully, requiring attending physician-level expertise. Efficacy studies supporting the use of PA catheterization in children undergoing congenital heart surgery are scarce in the existing literature. Therefore, risks incurred by PA catheter placement should be well taken into account.

**Technique.** The previously mentioned consensus statement, as well as the guidelines set by the American Society of Anesthesiologists task force, recommends that PA catheters should only be used by suitably experienced personnel to minimize complications, thus requiring adequate supervision throughout the procedure [117]. The selection of a PA catheter should be based on clinical need and patient size. To obtain maximal benefits, a PA catheter with oximetry and thermodilution CO measurement capabilities is desirable. Commercially available catheters equipped with these functions are 5.5 or 7.5 Fr in size and thus require a 6 or 8 Fr introducer sheath, respectively. A 5.5 Fr PA catheter should be used in patients up to approximately 40 kg in weight. Because of the direct path and curvature of the catheter, appropriate sites of insertion are the right IJV, left SCV, and FVs.

After full barrier precautions are taken and using the Seldinger technique following guidelines described earlier for percutaneous central catheter insertion, insert an introducer sheath into a central vein. The balloon integrity should be tested before insertion by inflating the recommended volume of air. Insert a flexible sterile sleeve before placement to protect the PA catheter outside the body and to allow for sterile repositioning later. Connect, flush, and calibrate the PA and CVP ports before insertion. Advance the catheter as far as the RA with the balloon deflated, then inflate the balloon and advance the catheter into the PA while observing the pressure tracing. The catheter’s advancement toward the tricuspid valve is signified by enlarging V waves on the CVP tracing. The catheter passes through the tricuspid valve during diastole and the characteristic RV trace becomes visible on the PA tracing, with no dicrotic notch and moderate diastolic pressure. Hasten advancement of the catheter through the RV because of the propensity for dysrhythmias. The diastolic pressure increases and the dicrotic notch becomes apparent as the...
catheter tip passes through the pulmonary valve. Gently advance the catheter until a pulmonary capillary wedge pressure (PCWP) tracing is obtained, at which point the balloon should be deflated so that the PA tracing returns. It may be necessary to reduce or remove any redundant length or loop in the RA or RV by slowly withdrawing the catheter 1–2 cm. The balloon can then be reinflated to determine the minimum inflation volume necessary to obtain a wedge pressure tracing. The best position for the catheter tip is where the full or near-full inflation volume (0.5–1.5 mL) produces a wedge pressure tracing. Advancement of the catheter to the PA should be relatively rapid because prolonged manipulation may result in loss of catheter stiffness, thereby causing coiling in the RV or difficulties in catheter advancement. When difficulty advancing the catheter through the pulmonary valve is encountered, counter-clockwise rotation of the catheter, along with positioning the patient with the right side down, may result in successful placement. Alternatively, TEE may be used to visualize and guide the PA catheter. The PA pressure should always be monitored with the waveform displayed on the monitor so that migration of the catheter into the distal PA or RV can be detected immediately. Leaving the catheter in the wedged position undetected can lead to particularly serious complications such as PA rupture or pulmonary infarction. The catheter should be withdrawn several centimeters during the bypass period to reduce the risk of PA perforation.

Specific information that can be gathered with regular PA catheters includes PA pressure (systolic, diastolic, and mean), PCWP, RA pressure, mixed venous gases, and CO by thermodilution. Measurement of the PCWP is important because it is a reasonable estimate of left atrial pressure (LAP), which in turn is an estimate of left ventricular end-diastolic pressure (LVEDP). The assumption that PCWP reflects LAP is only valid if patency of vascular channels between the distal port of the PA catheter and the left atrium is ensured. This will occur only in dependent portions of the lung (West’s zone 3), where pulmonary venous pressure exceeds alveolar pressure. Fortunately, with the patient in the supine position, a large portion of the lung is functioning in zone 3, and PA catheters will preferentially float into zone 3. To avoid erroneous readings, the PCWP should be measured at end expiration. The PCWP may not accurately reflect LVEDP in the presence of pulmonary venous or arterial hypertension, mitral valve disease, or positive end-expiratory pressure. The LVEDP is an index of left ventricular end-diastolic volume, the classic measure of left ventricular preload. The relation between left ventricular end-diastolic pressure and volume is best described by the left ventricular compliance curve, which is non-linear and is affected by many factors, such as ventricular compliance. Because TEE can provide more precise information regarding ventricular volume status, the usefulness of measuring PCWP becomes questionable.

Cardiac output can be measured with the standard thermodilution technique. In brief, a thermodilution PA catheter is connected to a CO monitor, a known amount of solution (injectate) of known temperature is rapidly injected into the proximal lumen of the catheter, this cooler-than-blood temperature solution mixes with the surrounding blood, the temperature is measured downstream in the thermistor on the PA catheter, and a decrease in temperature is recorded. The magnitude of the temperature change depends on the amount of blood that mixes with the injectate, and hence CO. The CO computer constructs a time–temperature curve to calculate CO from the area under the curve (AUC). When CO is low, more time is required for the temperature to return to baseline, producing a larger AUC. In contrast, with high CO, the injectate is carried more quickly through the heart, and the temperature returns to baseline faster, producing a smaller AUC. Thus, CO is inversely proportional to the AUC. Several factors may affect bolus CO determination: inaccurate temperature and volume of the injectate, rapid intravascular volume infusion during measurement, timing during the respiratory cycle, inaccurate computation constant, and thermal instability during the immediate post-bypass period. In addition, the presence of an intracardiac shunt can lead to erroneous CO values. For example, a left-to-right intracardiac shunt will cause recirculation of the injectate and create a larger AUC (decreased peak height and slower return to baseline), providing an erroneously low CO reading. A right-to-left shunt will have the opposite effect, providing an erroneously high CO reading. Therefore, the presence of an intracardiac shunt precludes the use of the thermodilution method to calculate CO. Technologic advances have produced PA catheters for continuous thermodilution CO monitoring using thermal indicators. Whereas the intermittent bolus technique uses cold injectate as the indicator, the new technology uses small energy impulses (warming of blood), which are emitted from a thermal filament directly into the bloodstream as the indicator; no fluid injection is required. These pulses of thermal energy emitted in a random on-off pattern change blood temperature, which is then detected by the thermistor at the tip of the PA catheter. Using a proprietary algorithm to analyze the thermal signal measured at the thermistor, a time–temperature curve is generated to calculate CO from the AUC. Typically, the displayed value for CO is updated every 30 seconds and represents the average CO over the previous 3–6 minutes. In this sense, this technology provides continual, frequently updated CO values.

Once CO is measured, systemic and pulmonary vascular resistances can be calculated. According to Ohm’s law, vascular resistance equals the pressure drop (pressure difference between the upstream and downstream circulation) divided by blood flow (CO). This equation is based on the assumptions that blood flow is steady-state, continuous, and laminar, and blood vessels are rigid conduits. This may be unrealistic for the pulmonary circulation, because pulmonary blood flow may cease at end diastole and pulmonary vessels are distensible [118]. Therefore, pulmonary vascular resistance calculated by
PA catheters may have limited value, although it is widely used; interpretation should be performed with caution. Other hemodynamic parameters [119–124] that can be calculated by PA catheter are listed in Table 10.6.

In addition to calculated hemodynamic variables, PA catheters can also provide important information regarding oxygen delivery and consumption, which may be used to guide therapy in critically ill children with low-CO syndrome. Because the arterial oxygen content is relatively constant under conditions of regular gas exchange, the major reflection of alterations in tissue oxygen extraction is SvO₂ [125]. If oxygen delivery is compromised to the periphery, tissues will increase their extraction of oxygen to compensate for reduced oxygen delivery. This will result in a decrease in SvO₂. Therefore, SvO₂ is an indirect indicator of the adequacy of tissue oxygenation, or a reflection of the balance between oxygen requirement and oxygen delivery. The relation between SvO₂ and CO can be shown by the modified Fick equation:

\[
\text{SvO}_2 = \frac{\text{SaO}_2 - \text{VO}_2}{1.34 \times \text{Hb} \times \text{CO}}
\]

where \(\text{SaO}_2\) is the arterial oxygen saturation, \(\text{VO}_2\) is the rate of oxygen consumption, and \(\text{Hb}\) is the hemoglobin concentration. From this equation, it is apparent that \(\text{SvO}_2\) varies directly with \(\text{CO}\), \(\text{Hb}\), and \(\text{SaO}_2\) and indirectly with metabolic rate (oxygen consumption).

A fiberoptic-equipped PA catheter allows for continuous monitoring of SvO₂ to guide timely therapeutic interventions during the perioperative period. Interpretation of SvO₂ may become difficult under conditions of intracardiac shunt, peripheral arterial venous shunt, sepsis, and cirrhosis.

**KEY POINTS: PULMONARY ARTERY CATHETERIZATION**

- A PA catheter should only be indicated in selected patients with CHD. Experienced physicians should directly supervise PA catheterization and its maintenance to avoid serious complications and erroneous interpretation of the data.
- Available sizes of PA catheter are a limiting factor for percutaneous insertion in children.
- In addition to hemodynamic parameters derived from the PA catheter, oxygen wellness should be calculated to direct therapy in ill children with low CO.

**Interpretation of intravascular pressure waveforms**

The information derived from intravascular catheters exceeds that of merely monitoring an absolute number; it is enhanced by observing the waveforms themselves. Accurate interpretation of the waveforms requires some understanding of the mechanical and electronic technical components of pressure monitoring. Pressure waves in the arterial and venous systems represent the transmission of forces generated in the ventricles. Measurement of these forces requires their transmission to a device that converts mechanical energy into electrical signals, which are processed and displayed. A system for intravascular pressure monitoring consists of intravascular catheters, fluid-filled tubing, connectors, transducers, amplifiers, and display devices. Understanding this system is a prerequisite for interpreting pressure waveforms. Although the use of commercially available, disposable transducer kits is common practice these days, the shortest possible, large-bore, stiff, plastic tubing should be tailored to the patient’s size. Minimization of the number of stopcocks and connections will improve the fidelity of the transmitted pressure wave [126]. It is imperative that the tubing system be thoroughly flushed before use to eliminate air bubbles or clots. In addition, it is important to recalibrate at the RA level (mid-axillary line) periodically to correct for transducer “drift.” Ringing and damping are two common sources of erroneous data acquisition from pressure monitoring and are associated with problems of dynamic accuracy [127–129]. Because a pressure monitoring system has resistance, inertia, and compliance, it can oscillate or “ring,” that is, overestimate the systolic pressure and underestimate the diastolic pressure. A system that is ringing (underdamped) results in higher systolic pressure and lower diastolic pressure. In contrast, a damped system provides lower systemic pressure and higher diastolic pressure. In the face of either ringing or damping, mean pressure is preserved and provides an accurate number. If the dynamic response of a system is in question, mechanical devices (e.g., a Resonance OverShoot Eliminator [ROSE™]; Argon Medical Devices, Inc., Plano TX, USA; Accudynamic®, Abbott Critical Care Systems, Abbott Park IL, USA) can be incorporated to alter the resonance frequency and/or damping factor of the transducer system [130,131]. The resonance frequency can be tested by flushing the system with a pressurized bag of heparinized saline, stopping abruptly, and observing the number and amplitude of oscillations required to return to baseline waveform (dynamic response) [132]. Proper damping is indicated by one oscillation below and one oscillation above the mean before returning to normal.

**Arterial pressure waveform**

Regular cardiac rhythm and the presence of CO can be confirmed by observation of the waveform on the monitor display. This is useful when prolonged use of electrocautery disturbs the ECG trace. Steep upstroke of the waveform implies good ventricular function, whereas slow upstroke may indicate poor contractility, left ventricular outflow tract obstruction, or peripheral vasoconstriction. The area under the systolic portion of the pressure curve is proportional to the stroke volume [133]. The position of the dicrotic notch is associated with changes in peripheral
Table 10.6  Normal values of hemodynamic and oxygen parameters

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</tr>
<tr>
<td>LVO/OBSA</td>
<td>2.0–4.0</td>
<td>3.5–6.5</td>
<td>3.0–7.1</td>
<td>3.3–6.9</td>
<td>L/min</td>
</tr>
<tr>
<td>RVCO/BSA</td>
<td>3.0–4.4</td>
<td>3.6–5.8</td>
<td></td>
<td></td>
<td>L/min</td>
</tr>
<tr>
<td>LVEDV – LVE5V or CO/HR</td>
<td>5–13</td>
<td>18–32</td>
<td>13–60</td>
<td>47–65</td>
<td>mL/beat</td>
</tr>
<tr>
<td>LVS/BSA</td>
<td>40–75</td>
<td>31–55</td>
<td>37–70</td>
<td>42–76</td>
<td>mL/beat</td>
</tr>
<tr>
<td>LVS × 100/LVEDV</td>
<td>45–81</td>
<td>46–71</td>
<td>47–77</td>
<td>47–78</td>
<td>%</td>
</tr>
<tr>
<td>RVSV × 100/RVEDV</td>
<td>59–73</td>
<td>39–63</td>
<td>55–73</td>
<td></td>
<td>%</td>
</tr>
<tr>
<td>(MAP – PCWP) × SV × 0.0136</td>
<td>20–40</td>
<td>30–62</td>
<td></td>
<td>45–60</td>
<td>g/beat</td>
</tr>
<tr>
<td>(MAP – CVP) × 80/CO</td>
<td>2800–4000</td>
<td>1200–2800</td>
<td></td>
<td>800–1200</td>
<td>dyne-sec</td>
</tr>
<tr>
<td>&lt; 2000–3200</td>
<td>&lt; 40–320</td>
<td></td>
<td></td>
<td>&lt; 250</td>
<td>dyne-sec</td>
</tr>
<tr>
<td>RVEDV</td>
<td>31–47</td>
<td>57–83</td>
<td></td>
<td>100–160</td>
<td>mL</td>
</tr>
<tr>
<td>Arterial O₂ content (CaO₂)</td>
<td>1.34 × Hb × SaO₂ + 0.0031 × PaO₂</td>
<td>15–18</td>
<td>16–18</td>
<td>18–20</td>
<td>mL/dL</td>
</tr>
<tr>
<td>Mixed venous O₂ content (CvO₂)</td>
<td>1.34 × Hb × SvO₂ + 0.0031 × PvO₂</td>
<td>11–14</td>
<td>12–14</td>
<td>13–16</td>
<td>mL/dL</td>
</tr>
<tr>
<td>Arterial-venous oxygen difference (CaO₂ – CvO₂)</td>
<td>4–7</td>
<td>4–6</td>
<td>4–5.5</td>
<td>mL/dL</td>
<td>[122]</td>
</tr>
<tr>
<td>Pulmonary capillary O₂ content (CcO₂)</td>
<td>1.34 × Hb × SCcO₂ + 0.0031 × PcO₂</td>
<td>16–19</td>
<td>17–19</td>
<td>19–21</td>
<td>mL/dL</td>
</tr>
<tr>
<td>Pulmonary shunt fraction (Qs/Qt)</td>
<td>100 × (CcO₂ – CaO₂)/(CcO₂ – CvO₂)</td>
<td>2–8</td>
<td></td>
<td>%</td>
<td>[122]</td>
</tr>
<tr>
<td>O₂ delivery index (DO₂, f)</td>
<td>CO × CaO₂ × 10/BSA</td>
<td>450–750</td>
<td>450–700</td>
<td>450–640</td>
<td>mL/min</td>
</tr>
<tr>
<td>O₂ consumption index (VO₂, f)</td>
<td>(CaO₂ – CvO₂) × CI × 10</td>
<td>150–200</td>
<td>120–200</td>
<td>85–170</td>
<td>mL/min</td>
</tr>
</tbody>
</table>

HR, heart rate; LV, left ventricle; RV, right ventricle; CO, cardiac output; CI, cardiac index; SV, stroke volume; SVI, stroke volume index; SWI, stroke work index; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance; EDV, end-diastolic volume.
vascular resistance. In infants, a normal dicrotic notch is found in the upper half of the pressure wave. A dicrotic notch located high on the downslope of the arterial waveform may indicate increased systemic vascular resistance, whereas one located lower on the downslope may indicate low resistance. A low-placed dicrotic notch with a steeper diastolic downslope is also observed in hypovolemic patients. A decrease in both peak systolic pressure and pulse pressure, which is accentuated by positive pressure ventilation, is an early indicator of hypovolemia or cardiac tamponade. Aortic stenosis will result in a pressure waveform with a slow-rising upstroke, delayed peak, and narrow pulse pressure, whereas aortic regurgitation will result in a steep upstroke, bifid peak, widened pulse pressure, and low diastolic pressure. Low diastolic blood pressure can also reflect excessive distal “run-off,” as in patients with large patent ductus arteriosus. A sudden increase in diastolic pressure occurs on ligation of the ductus because diastolic run-off into the PA ceases.

The systolic pressure is higher in the more distal arteries due to the wave-reflection phenomenon [134]. As the pressure wave passes down the arterial tree, it is modified by arterial narrowing, loss of arterial elastic tissue, and the addition of reflected waves, until it reaches the distal catheter. With distal progression, pulse wave amplification will produce a higher peaked pressure wave with a slightly higher systolic pressure. This is most pronounced in the arteries of the foot, where the systolic pressure may be 5–15 torr higher than in the ascending aorta (Figure 10.13) [135]. Diastolic and mean pressures change very little with progression. This concept is important for interpreting arterial pressure tracings. The post-bypass arterial tracing is frequently damped with catheters in small distal arteries (e.g., radial or foot arteries), probably due to vasoconstriction induced by CPB [136]. This usually does not last long after bypass; however, it can be troubling to observe, particularly during potentially critical periods of weaning from bypass. For long and difficult surgeries with long bypass or cross-clamp times, it may be prudent to place catheters in larger, more central arteries (e.g., femoral or umbilical) or to ask the surgeon to measure pressure directly in the aortic root from the aortic cannula immediately after bypass to obtain an accurate arterial pressure.

Failure of arterial pressure monitoring during congenital heart surgery is possible. Reasons for failure can include arterial spasm, kinking or clotting of the catheter, compression of an aberrant right subclavian artery by a TEE probe, or compression of the axillary artery by a sternal retractor. A back-up manual blood pressure cuff should be always available. Alternatively, placement of a femoral artery catheter may be performed by the surgeon.

Central venous and left atrial waveforms

The usual sites of filling pressure measurement are the CVP (right atrial pressure) and LAP. In the presence of normal tricuspid and mitral valves, the CVP and LAP reflect their respective ventricular end-diastolic pressures. Normal atrial pressure traces have three positive waves, A, C, and V, corresponding to atrial contraction, closure of tricuspid or mitral valve, and ventricular contraction (Figure 10.14). The right atrial V wave is normally lower in amplitude than the A wave; however, in patients with atrial septal defect, the higher LAP may be transmitted to the RA during atrial filling, causing the right atrial A and V waves to be equal in amplitude. Changes in the components of atrial pressures may indicate pathologic ventricular function and cardiac rhythm. For example, a large V wave in the CVP may be caused by severe tricuspid regurgitation, which may reflect right heart failure, pulmonary hypertension, or right ventricular ischemia. Similarly, a large V wave in the LAP indicates mitral valve regurgitation. Disappearance of the A wave

![Figure 10.13](image1.png)

**Figure 10.13** Progression of the arterial pressure tracing from the root of the aorta to more peripheral arteries. Pulse-wave amplification produces a higher systolic peak and slightly lower diastolic pressure in the smaller distal arteries, especially the dorsalis pedis. (Source: Reich et al. [135]. Reproduced with permission of Elsevier.)

![Figure 10.14](image2.png)

**Figure 10.14** Central venous pressure waveform. The A wave represents increased atrial pressure. The C wave represents closure of the tricuspid valve. Downward movement of the ventricle during systolic contraction forms the X descent. The V wave arises from the pressure produced when the blood filling the right atrium comes up against a closed tricuspid valve. Opening of the tricuspid valve in diastole, with blood flowing into the right ventricle, produces the Y descent.
with appearance of an enlarged V wave indicates lack of atrial contraction because of loss of atrioventricular synchrony, as in junctional ectopic tachycardia, supraventricular tachycardia, atrial fibrillation, or atrial flutter (Figure 10.15). This is particularly important in discerning pathologic tachyarrhythmia from sinus tachycardia. In the face of rapid heart rate, the P wave of the ECG is often indiscernible, making cardiac rhythm from ECG difficult to determine. In contrast, the presence of an A wave in atrial pressure waveforms assures atrioventricular synchrony.

The transducer position is particularly important for accurate measurement of atrial pressure, and it is usually set at the level of the RA. Slight position changes can easily provide erroneously high or low numbers because both the CVP and LAP measure low pressures of several cmH\textsubscript{2}O. Constant vigilance is necessary to keep the transducer level in the correct position and accurately calibrated.

**KEY POINTS: INTERPRETATION OF INTRAVASCULAR PRESSURE WAVEFORMS**

- Observation of the pressure waveform *per se* can provide additional diagnostic information and should be displayed continuously during pressure monitoring.
- Common errors made in data acquisition from arterial catheters include calibration error, improper calibration (gain), underdamping, and overdamping.
- In the presence of normal tricuspid and mitral valves, the CVP and LAP reflect their respective ventricular end-diastolic pressures.

**New techniques in pediatric intravascular monitoring**

**CO monitoring**

Because traditional percutaneous, balloon-tipped PA catheterization is limited in small children, and those with intracardiac shunting, several other recently derived methods invented for adults to measure CO and oxygen delivery in patients with CHD have been applied to infants and children [137]. Lithium dilution CO (LiDCO) uses a standard central line in the SVC or even a peripheral IV catheter, and a special femoral artery catheter equipped with a lithium-detecting electrode. A dilute solution of lithium chloride is injected into the vein, and arterial blood is withdrawn into the lithium electrode. The cardiac index is related to the AUC of the change of lithium concentration. This method has been demonstrated to have reasonable correlation with thermodilution CO in children after congenital heart surgery. In a study of 48 measurements in 17 patients weighing 2.6–34 kg, the correlation between LiDCO and thermodilution CO was good ($r^2 = 0.96$), and the mean bias was $-0.1 \pm 0.31 \text{ L/min}$ [138].

Transpulmonary thermodilution CO uses a similar principle as LiDCO, except with temperature as the indicator instead of lithium concentration. Cold saline is injected into a CVC, and via a thermistor placed in a femoral artery, a time–temperature curve is derived, which correlates reasonably well with standard thermodilution CO as measured by a standard PA catheter [139]. Both lithium and any thermodilution method are limited to patients without any intracardiac shunting, significantly restricting their use in CHD.

Yet another newer method is pulse contour analysis of the arterial waveform (PiCCO), which relates the contour and AUC to the stroke volume, and thus the CO. This continuous method is periodically calibrated using the transpulmonary thermodilution CO as described above (again making the method invalid with intracardiac shunting), and demonstrates a good correlation with transpulmonary thermodilution in a study of 24 pediatric patients after cardiac surgery ($r^2 = 0.86$, mean bias $0.05 \pm 0.41 \text{ L/min/m}^2$) [140]. More recent data are lacking, there are no pediatric outcome studies, and although a recent review concludes that both lithium dilution and transpulmonary thermodilution methods have good correlation with thermodilution CO, these methods have not yet found their place in pediatric cardiac surgical cases [141].
Central venous oxygen saturation monitoring

Monitoring of intravascular oxyhemoglobin saturation using reflectance catheters has been used in the umbilical artery, PA, and adult-sized CVCs for a number of years, but only recently have standard pediatric sized 4 and 5 Fr, double- and triple-lumen CVCs become available for routine use to measure central venous oxygen saturation (ScvO$_2$) in pediatric patients. The advantage of this method is that it is a measure of oxygen delivery that is independent of intracardiac shunting, and thus may have better utility in the CHD patient. In 16 pediatric patients undergoing cardiac surgery, Liakopoulos et al. demonstrated good correlation between ScvO$_2$ as measured with the catheter and with blood co-oximetry ($r^2 = 0.88$, bias $-0.03 \pm 4.72\%$, precision $-8.02\%$ to $+8.09\%$) [142]. Three more recent studies in 75 critically ill infants and children undergoing cardiac or other major surgery report a wider range of correlation ($r^2 = 0.28$ to 0.93), bias ($-1.1\%$ to $+2.6\%$), and precision ($-18\%$ to $+23\%$) [143–145]. Outcome data are lacking for this technique, but it has been useful as an adjunct for continuous trend monitoring of oxygen delivery in major cases.

Complications of vascular access

Incidence and risk factors

Central catheterization remains a mandatory procedure in many critically ill pediatric patients. Notwithstanding its certain advantages (e.g., large-bore catheters, monitoring, drug administration), central catheterization carries risks of serious complications. These can be categorized into mechanical or insertion-related complications (e.g., inadvertent arterial puncture, malposition, arterial catheterization, arrhythmia, hematoma, pneumothorax, hemothorax, cardiac tamponade) and maintenance-related complications (e.g., obstruction, occlusion, systemic venous air embolization, infection). If detected promptly, minor complications can be readily corrected; however, some (pneumothorax, hemothorax, cardiac tamponade) may be life-threatening. Sufficient knowledge and preparation, diligent technique, skill, and experience are obligatory.

The incidence of all vascular access-related complications is difficult to ascertain from published research, but numerous case reports and studies have addressed this issue. Among early mechanical complications, the most frequent are arterial puncture, malposition, artery catheterization, and hematoma. The most frequent life-threatening complications are pneumothorax, cardiac tamponade, and hemothorax. The most frequent catheter maintenance-related complications are obstruction, occlusion, and sepsis.

The relationship between insertion site and complications has been well studied [146–148]. The SCV approach is anatomically more prone to early insertion-related complications [149] than IJV or FV catheterizations; however, significantly more maintenance-related problems develop in children with indwelling femoral catheters [148].

Operator experience appears to influence the rate of complications. In one study, resident anesthesiologists caused significantly more complications, both common and rare, than their senior colleagues; however, when closely supervised, the rates of acute mechanical complications [88], deep vein thrombosis (DVT), and infection were lower. Lower complication rates and higher success rates were obtained after sufficient training in landmark and ultrasound-guided techniques [89].

In general, risk factors for central venous catheterization-related complications include previous unsuccessful insertion attempts, more than two punctures, inexperience, body mass index $< 20$ and $> 30$, previous catheterizations, previous catheterization attempts, previous operations, radiotherapy, severe dehydration or hypovolemia, and large catheter size [149]. In neonates, catheter insertion can be challenging due to anatomic difficulties [150]. In older children, insertion-related problems appear not to be associated with age; however, maintenance-related complications are more commonly observed in younger children [146]. Similar to the adult population, duration of catheterization is closely related to frequency of maintenance-related complications in pediatric patients [148].

Totally implantable central catheters (ports), PICCs, and tunneled external central catheters (e.g., Broviac catheters) have been used more often in critically or chronically ill pediatric patients. In a study summarizing implanted catheter-related issues, the overall rate of reported complications was 31%; leakage was a specific problem necessitating reinsertion or repair. Infections were observed in 6% of patients with implanted central catheters and developed more than 30 days after catheterization [151]. When Broviac and clampless valved catheters were compared, malfunction was more frequently observed in the former group, whereas catheter displacement was more commonly found in the latter [152].

Thrombosis

Catheter thrombotic occlusions and catheter-related thrombosis in pediatric patients have become increasingly prevalent. The incidence of central catheter-related DVT has been reported to be 0.13/1,000 catheter-days [153]. This is one of the most frequent complications, especially among infants. Central venous thrombosis is reported to occur in 5.8% of neonatal patients, 10 times that of older patients; 40–50% of central venous thrombosis in this group occurs after congenital heart surgery [154]. A recent study examining the incidence of asymptomatic CVC-related DVT in pediatric ICU patients revealed that age was independently associated with DVT; children aged more than 13 years were more likely to develop DVT than those aged less than 1 year [155].

Factors contributing to the risk of thrombosis include large-bore catheters in small vessels (i.e., larger than 4 Fr in
small infants), duration of cannulation exceeding 7 days, venous stasis due to extreme fluid restriction or low CO, infusion of high-osmolarity fluids, and hypercoagulable states.

Indwelling central catheters act as additional foci for clot formation, and migrating clots can obstruct pulmonary, coronary, and cerebral vessels, leading to life-threatening events. Rare conditions, such as arteriovenous malformations, may serve as sources of emboli; the brain is at particular risk of paradoxical embolism, further facilitated by the presence of right-to-left intracardiac shunts and pulmonary vascular abnormalities [156].

Immediate consequences of SVC thrombosis include SVC syndrome [12] with increased intracranial pressure and chylothorax due to ineffective drainage of the thoracic duct. Thrombosis of the IVC results in renal and intestinal dysfunction, ascites, and edema of the lower abdomen and extremities [146]. Assess carefully for signs of thrombosis; suspicion of thrombosis should be evaluated by ultrasound examination [157].

A wide range of options is available for the management of catheter-related thromboembolism. These include removing the catheter, heparinization, administration of thrombolytic agents such as tissue plasminogen activator and urokinase, antithrombin III replacement, and surgical thrombectomy. In children, 5,000 IU of intraluminal urokinase was reported to be as effective as 25,000 IU in resolving withdrawal occlusion in partially implanted central catheters [158]. Systemic urokinase may rescue a significant proportion of central catheters refractory to intraluminal urokinase or those apparently completely occluded.

Prevention of SVC thrombosis is crucial, and avoiding SVC catheterization in patients weighing less than 4 kg is often preferable. In children undergoing superior cavopulmonary anastomosis, EJV catheterization reliably predicts IJV and pulmonary arterial pressures and may obviate the risk of life-threatening cavopulmonary thrombosis [38]. Thrombosis is also associated with higher rates of infection [159,160]. Heparin-bonded catheters can decrease the rate of thrombosis and do not increase the risk of bleeding [159,161]. In patients with occlusion of central veins due to previous catheters, magnetic resonance venography can be useful in identifying patent veins for future interventions [162].

Thrombosis or dissection of an artery is a serious complication that must be treated immediately. It is important to inspect the distal extremity after catheter placement, comparing it with the contralateral extremity, assessing capillary refill, and to palpate distal pulses. Place a pulse oximetry probe distal to the catheter to serve as a continuous monitor for potential vascular insufficiency. Transient compromise of perfusion immediately after placement of a catheter, due to arterial spasm or during low output states, may be observed. If perfusion of an extremity is significantly compromised, removal of the catheter, use of vasodilators, warming the extremity, administration of heparin or thrombolytics, surgical consultation, thrombectomy, or surgical reconstruction is indicated.

Neonatal arterial thrombosis has become more common with the use of umbilical artery catheters [163]; however, catheter-induced aortic thrombosis is rare. In a study of approximately 4,000 infants with an inserted umbilical artery catheter, 44 developed major thromboembolic problems requiring varying degrees of surgical management [164]. The most common location of arterial thrombosis associated with umbilical artery catheterization in neonates is the abdominal aorta [165].

**Infection**

Catheter-related sepsis can result in significant morbidity, increased mortality, prolonged ICU stay, and increased expense. Numerous studies have described the incidence of risk factors for, and management of catheter-related infections. Sepsis was reported in 5.8–7.6% of pediatric patients, and the rate of catheter-related bloodstream infections (CRBSIs) was 0.1–6.4 infections/1,000 catheter-days [143,166,167]. The incidence of arterial catheterization-related infections in the pediatric population is very low; the calculated rate is 6.2% [168]. The pathogen mainly responsible is Staphylococcus epidermidis, and its colonization is not dependent on the catheter insertion site [146].

Risk factors for CRBSIs include weight less than 8 kg, cardiac failure, cancer, silicone catheters, guidewire exchange catheterization, obstructed catheters, and more than 12 days of catheter placement [167]. A higher incidence of central line-associated bloodstream infections was found in children between 1 and 2 years of age [169]. The safe period for an indwelling CVC is 3 days in infants less than 12 months old and 6 days in older children; the infection rate increases if catheters are left in place for more than 10 days [170]. The number of catheter lumens does not appear to influence the rate of this complication [43].

Several strategies may be used to reduce catheter-related infections [171]. First is the use of full barrier precautions (e.g., sterile gown, mask, gloves, and careful aseptic technique during insertion). Second, a potent antiseptic solution should be used for skin scrubbing and during redressing of the insertion site every 3 to 7 days. In addition, systemic antibiotic administration or antibiotic bonding to the resin of the catheter may be advantageous (Box 10.1).

Chlorhexidine has been shown to be superior to other antiseptic solutions and is being used more frequently for catheter insertion-related antisepsis. Novel chlorhexidine-impregnated dressings or chlorhexidine-impregnated sponges are safe and effective in preventing CRBSIs and non-catheter-related bloodstream infections in neonates requiring prolonged central venous access, and their use significantly reduces the rates of central catheter colonization in infants and children after cardiac surgery [172–174]. Although it provides effective skin protection, chlorhexidine may cause contact dermatitis, particularly in low-weight infants, and some cases of anaphylactic reaction to
chlorhexidine-impregnated catheters have also been reported [175].

The use of antibiotics for prevention of central catheterization-related infections has not yet been supported by strong evidence. Although vancomycin added to the solution used for total parenteral nutrition effectively reduced catheter-related sepsis in a neonatal ICU and offered potential benefits (e.g., fewer catheters, earlier weight gain), its widespread implementation has not been recommended [176]. The addition of vancomycin to heparin flush solutions did not reduce bacteremia with vancomycin-susceptible organisms [177]. In a meta-analysis of 21 randomized controlled trials comparing the incidence of specific bacterial and fungal species colonization on minocycline/rifampicin-impregnated catheters, the proportion of all colonized antibiotic-impregnated catheters found to harbor Candida species was greater than the proportion of all colonized non-impregnated standard catheters [178]. Commercially available antimicrobial catheters may become colonized with distinct microbial flora, probably related their antimicrobial spectrum of activity [178].

Suspected CRBSI should be addressed by peripheral blood culture and blood culture from the central catheter. Remove the catheter when possible and send the tip for bacterial culture. Design antibiotic therapy empirically against the most common institution-specific pathogens and provide coverage for S. epidermidis. Proper education may also reduce infection frequency; in a quasi-experimental study designed to improve the quality of clinical practice in a neonatal ICU, the rate of CRBSIs decreased from 8.4 to 1.28 cases/1,000 central line-days [179].

**Malposition/perforation**

Perforation of a vein or the heart can occur during CVC placement or any time thereafter. The cause of perforation can be a needle, guidewire, dilator, or the catheter itself. Malpositioning of the CVC may not necessarily lead to complications per se, but a catheter tip in the RA [180,181] or not parallel to the SVC clearly predisposes to subsequent complications. Other predisposing factors for CVC perforation include a left-sided approach, use of a guidewire end without a flexible tip, a stiffer catheter, and “long-arm” CVC inserted in the basilic or cephalic veins. With left-sided lines, the catheter tip is frequently at a 45–90° angle to the SVC or atrium. Models have shown that this position is more likely to lead to great vessel perforation [182]. Up to 5–10% of patients with CHD have a left SVC [183], which drains most often into the coronary sinus or left atrium; both of these sites are undesirable for catheterization. An ideal position is in the mid-SVC, with the tip parallel to the vein wall. Long-arm CVCs tend to be more mobile than other CVCs, thus increasing the possibility of the catheter tip migrating into the RA with arm movement. The material of which catheters are made may also be associated with incidence of this complication; soft polyurethane or silicone catheters are much less likely to perforate than stiffer polyethylene catheters [184].

Inability to consistently aspirate blood, abnormal waveform, or signs or symptoms of pericardial tamponade or hemothorax indicate perforation. Treatment involves aspiration of as much blood as possible through the catheter and establishment of alternate access; intravascular volume replacement; and drainage of the pericardial or pleural blood by needle or surgical exploration. Confirmation of catheter tip location with an anteroposterior radiograph after insertion is obligatory.

The mid-SVC, above the pericardial reflection, is the recommended position for the catheter tip; however, positioning a multi-lumen catheter too cephalad in the SVC may result in a situation in which one of the
proximal ports is not inside the jugular vein, leading to extravascular extravasation of important or caustic drugs or fluids. Many studies of catheter placement in children have shown that the internal jugular route results in tip placement in the SVC or RA 98%–100% of the time, whereas the subclavian route results in a 5%–15% rate of catheter malposition (i.e., across the midline in the contralateral brachioccephalic vein or up the ipsilateral IJV).

Accurate CVP measurements are generally obtained with IVC catheters, whether placed above or below the diaphragm. Umbilical venous catheters should be placed above the diaphragm at the IVC–RA junction, but not in the RA, to ensure passage through the ductus venosus and a parallel position to the IVC wall [185].

Some rare, inadvertent, CVC placement locations have been reported. Catheters may pass into the superior intercostal, thymic, azygos, or ascending lumbar veins or even into the liver parenchyma, depending on the insertion site [186–188]. Dural puncture, intrathecal catheterization, or extradural catheter insertion have also been reported [189–192]. In a case report, neurologic complications (paraplegia, urine retention, and milky cerebrospinal fluid) developed after abnormal placement of a catheter into the lumbar venous plexus via the left saphenous vein [188]. If malposition is strongly suspected, the catheter must be removed and the patient assessed for other complications.

Pneumothorax/hemothorax

Pneumothorax occurs in 7% of central venous catheterization cases [193], being most frequent with the subclavian approach (2.6%) [146], but it may also occur with the IJV approach (0.38%) [86], especially with low puncture sites. In four reported cases of hemothorax [194–197], the complication resulted in a fatal outcome in all cases. Perforation of the punctured vein, leading to pneumo- or hemothorax, may be caused not only by the advancing needle (as in the Seldinger technique), but also by guidewires, dilators, or relatively rigid catheters.

Pneumothorax and hemothorax can be avoided by cautious advancement of needles, guidewires, dilators, and catheters. An ultrasound guidance system greatly facilitates catheter insertion when used properly. The following tips may also be helpful:

- In the subclavian approach, it is important to advance the needle only during expiration.
- A very shallow approach, with the needle directed just posterior to the clavicle and at the sternal notch, is recommended.
- For the IJV, a higher puncture site and limit of caudal advancement of the needle to stop above the clavicle are preferable.
- Continuous aspiration with a saline-filled syringe should be performed as the needle is advanced.
- If air is aspirated, stop puncture attempts immediately and monitor carefully for compromise of ventilation and hemodynamics. Chest radiography should be performed, and pleural drainage should be initiated if indicated. After sternotomy, the pleura can be opened on the side where the pneumothorax is suspected or diagnosed.

Cardiac tamponade

Cardiac tamponade is a severe complication of central venous catheterization and is closely related to catheter malposition and vessel perforation during puncture or placement. The incidence of cardiac tamponade after pediatric cardiac surgery ranges from 0.04% to 7% [198]. Catheter characteristics (rigid polyethylene catheters are more likely to cause tamponade than flexible silicone or polyurethane catheters [181]) and vessel wall tear caused by an abnormally placed catheter might be associated with increased risk of tamponade, but detailed studies have not been carried out. Age-associated difficulties with catheter insertion may also be related to a higher risk. In a study of 10 children with cardiac tamponade, seven were infants, and most complications occurred during needle advancement, with symptoms developing within minutes to up to 12 hours after the procedure [199].

Inadvertent arterial puncture or catheter placement

Inadvertent puncture of the CCA during IJV catheterization is a well-recognized complication; however, other arteries, including the subclavian, vertebral, transverse cervical, and thyroid inferior arteries, are occasionally located behind the IJV and are at risk of perforation [197,200,201]. Some authors suggest identifying the presence of vertebral arteries to avoid accidental puncture during IJV catheterization in pediatric patients [95,97].

Inadvertent arterial puncture can nearly always be prevented by the use of ultrasound guidance. The presence of potential anatomic variations should be confirmed with ultrasound Doppler color flow imaging, and real-time, ultrasound-guided venipuncture should follow a preprocedural ultrasonographic assessment [95,97].

If this complication occurs, the following principles may be useful. After needle puncture, remove the needle immediately, elevate the area, and hold firm pressure for 5–10 minutes. A small-bore needle puncture of the carotid or femoral artery (e.g., 20 ga or smaller) is not usually an indication to cancel surgery. If a larger hole is created (i.e., a dilator and catheter have been placed), pressure transduction can be used to confirm the location. In this case, a discussion with the surgeon must ensue. Normally, the catheter can be removed and pressure held without consequences, unless a very large catheter was used (e.g., introducer sheath or large-bore CVP catheter), in which cases surgical exploration and repair should be undertaken. In most cases of elective cardiac surgery, it is prudent to postpone the surgery if a large hole has been made in the artery. Surgery can usually be performed safely 24 hours later, if no bleeding has occurred. If surgery must proceed after an unintended arterial puncture with a large needle
or catheter, sterile preparation of the site and inclusion in the surgical field are prudent to facilitate direct observation and access for repair during the surgery if indicated.

**Arrhythmias**

Central catheters and guidewires can cause arrhythmias. Too deep advancement of the catheter or guidewire has been associated with ectopic atrial tachycardia, especially with the catheter tip in the RA mechanically stimulating and potentially injuring the conduction system of the heart. Atrial fibrillation is also associated with CVC placement. Arrhythmias occur more commonly with passage of the guidewire. These include isolated PACs, supraventricular tachycardia, and, if the guidewire is advanced into the RV, premature ventricular contractions or even ventricular tachycardia or fibrillation.

For prevention, a marked guidewire should be used for IJV catheterization. Extreme care must be taken when passing a guidewire to stop advancement if significant arrhythmias are encountered, and when advancing the catheter over the wire. Guidewires must be advanced at as shallow an angle as possible, and in accordance with the body size of the patient. Pediatric patients at particular risk of arrhythmia are those with a known history of arrhythmia, cardiomyopathy, or RV hypertrophy [202]. Cardioversion is effective when atrial fibrillation or life-threatening supraventricular tachycardia develops [202,203].

**Systemic venous air embolus**

Systemic air embolus is a constant threat for patients with central or peripheral venous catheters and intracardiac shunting, particularly those with two ventricles and right-to-left shunting and infants with a single ventricle and obligate mixing of systemic and pulmonary venous return in the systemic ventricle. Air may lodge in the coronary arteries, especially the right, the PA, or the brain, leading to potentially serious consequences. The incidence of venous air embolization caused by central or peripheral IV catheters has not been studied in detail, and it is possible that this complication is vastly underestimated or even neglected [204].

Large air emboli can be observed by TEE or transcranial Doppler ultrasound, but prevention is most important. Extreme attention must be paid to avoid the introduction of air into the systemic venous circulation. Careful preparation of venous infusions includes the following: thorough de-airing of all infusions before connection; de-airing of continuous-flush central venous lines; air filters on continuous infusions; and careful technique when injecting drugs and fluids, which involves holding the syringe upright, flushing fluid from the proximal IV tubing, and aspirating and tapping the syringe before injection [205]. Constant vigilance, the use of TEE to monitor for intracardiac air and transcranial Doppler for systemic arterial air, and meticulous technique of catheter removal may reduce the risk of air embolus.

**Foreign bodies**

Embolization of catheter or guidewire fragments sheared off during difficult insertion procedures, and disrupted catheter fragments in response to repeated mechanical compression between the clavicle and the ipsilateral first rib have been reported [206,207]. The latter, known as “pinch-off” syndrome, develops occasionally after a long period of catheter indwelling (1 month to 3 years) and poses many treatment difficulties [207]. Prevention includes selection of alternative techniques (percutaneous supraclavicular or IJV approaches or ultrasound-guided catheterization of the axillary vein). If resistance is encountered when withdrawing the guidewire, the guidewire and the needle, or the catheter and the needle, must be withdrawn completely from the vessel together as a unit. Before insertion of long-term indwelling catheters (e.g., for home parenteral nutrition), information should be provided to patients and/or their caregivers regarding possible complications related to catheter shearing.

**Complications related to intracardiac catheters**

This category is unique to children undergoing congenital heart surgery because intracardiac catheters are rarely used in other situations. In a large retrospective study of 6,690 transthoracic intracardiac catheters in 5,666 pediatric cardiac patients over a 10-year period, there was an overall 0.6% incidence of serious complications, defined as significant bleeding or catheter retention [49]. The risk was greatest for PA catheters (1.1%, with three cases of severe cardiac tamponade and one death for 1,680 catheters) followed by left atrial catheters, then right atrial catheters. The authors concluded that the benefits of intracardiac catheters far outweigh associated risks if care is exercised in placing and removing them and if complications are recognized rapidly and managed aggressively. However, another study reported a relatively high complication rate (37%) of bleeding in 523 transthoracic intracardiac catheters (276 right atrial, 155 left atrial, 68 common atrial, and 24 RV or PA catheters), with the highest rate (47%) in left atrial catheters [208]. These bleeding events required intervention in 8.3% of the patients and caused hemodynamic compromise in 2.6%. To date, there have been no outcome studies available comparing transthoracic and percutaneous catheters.

**Other complications**

Chylothorax [209], phrenic nerve injury [210,211], vertebral arteriovenous fistula [212], brachial arteriovenous fistula [213], Horner’s syndrome [214-216], and tracheal puncture [217] have also been described. These complications can prevented by skilled personnel and the use of ultrasound-guided techniques to accurately identify vessel location.
**Key Points: Complications of Vascular Access**

- Complications associated with vascular access can be categorized into catheter insertion- and maintenance-related complications. The most common are arterial puncture and catheter obstruction, respectively.
- The most frequent life-threatening complication of central catheterization is pneumothorax.
- Insertion-related complications occur more frequently with the subclavian approach than with the IJV or femoral approach.
- Appropriate training in pediatric central catheterization, especially in ultrasound-guided techniques, can reduce complications.
- To avoid serious or life-threatening outcomes, risk factors for central catheterization-related complications in children and those for central catheterization-related bloodstream infections should be taken into consideration when planning the procedure.

**Conclusions**

Vascular access in children undergoing surgery for CHD can be challenging and presents a difficult task for pediatric anesthesiologists. Each needs to gain experience and proper technique to develop his or her own approach to vascular access. No one approach has been shown to be superior to another. However, there is accumulating data favoring ultrasound-guided catheter insertion and we believe this technique will become a standard practice for percutaneous central venous access because the importance of decreased complication rates, insertion time, and expense cannot be overemphasized. Attention to the details of vascular access is important for enhancing patient safety. This, along with a strategy to preserve access sites in small infants with single-ventricle physiology and who may need multiple cardiac surgeries, ultrasound-guided line placement and the use of antibiotic-impregnated catheters will improve the outcome of vascular access procedures.

**Selected References**

*A full reference list for this chapter is available at:*

http://www.wiley.com/go/andropoulos/congenitalheart


CHAPTER 11
Neurological Monitoring and Outcome

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Introduction

Operative management of the child with congenital heart disease (CHD) was largely refined to its current state in the decades prior to the year 2000, during which operative mortality improved substantially. Data from the metropolitan Atlanta congenital defects program showed a profound increase in 1-year survival of the most critical heart defects, including hypoplastic left heart syndrome (HLHS), truncus arteriosus, pulmonary atresia, tricuspid atresia and tetralogy of Fallot from 67% (1979–1993) to 83% (1994–2005) [1]. Predictably, the increased expectation of survival is accompanied by willingness to perform surgery on increasingly complex patients. A multi-institution comparison of survival rates by case complexity using the Risk Adjustment for Congenital Heart Surgery (RACHS) showed a shift of fewer RACHS category 1 cases (low complexity) and more RACHS category 3, 4 and 6 cases (higher complexity) between 1996 and 2004. Further, mortality of RACHS category 6 (predominantly Norwood stage I palliation for HLHS) cases decreased from 48% in 1996 to 17% in 2004 [2].

Despite these remarkable gains, survivors of complex CHD are at risk of having a characteristic array of neurodevelopmental deficits. These include poor impulse control, attention deficit, hyperactivity, mild language and cognitive deficits, and limited executive functioning ability [3–7]. Often appearing outwardly normal, children with such deficits perform poorly in academics, and lack employability; they suffer high rates of depression and poor quality of life [8–13]. The relative role of modifiable (acute neurologic injuries) and non-modifiable factors contributing to the neurologic abnormalities seen in patients with CHD is a subject of study and debate. This chapter, written for the anesthesiologist, has an understandable bias toward discussion of the potentially modifiable perioperative factors that have been associated with neurologic injury. The pediatric cardiac anesthesiologist should be familiar with acute, perioperatively acquired neurologic injuries in this population, and proposed strategies to avoid them.

Acute neurologic injury in the perioperative period has been quantified using magnetic resonance imaging (MRI) technology. Preoperative neurologic injuries visible
by MRI occur with an incidence between 20% and 40% in newborns with critical heart defects [7,14–16]. After surgery, 35–75% of patients will have a new lesion [17]. Despite differences in nomenclature of MRI findings, it is clear that the preponderance of new injuries seen after cardiac surgery in the infant occur in the white matter (see Figure 11.1) [14,15,18–21]. Most studies further specified the preponderant white matter lesion as periventricular leukomalacia, an injury that has been extensively described in preterm infants exposed to extrauterine life (see Figure 11.2). In the preterm population, periventricular leukomalacia is associated with reduction in brain growth and neurodevelopmental impairments with deficits similar to those described in children with critical heart lesions [22,23]. Current understanding of the pathogenesis of preterm periventricular leukomalacia posits that the preterm brain is susceptible to ischemia due to an incomplete redundancy of penetrating arterioles in the deep white matter, combined with a population of developing oligodendrocyte precursors with enhanced ischemic sensitivity [24–26]. This pattern of injury in the patient with CHD suggests that oxygen deprivation is the leading cause of intraoperative injury, not embolic or hemorrhagic injury as is more commonly seen in adults.

It has been assumed that improvements in hemodynamic management during cardiac surgery have the potential to mitigate neurologic injuries in children who require cardiopulmonary bypass (CPB). However, the management of CPB for infants and children has been challenging to study clinically due to wide practice variability and lack of inter-center consensus. Pump prime, flow rate, cardioplegia solutions and administration intervals, vasodilator therapy, steroid use, cooling and rewarming practices, blood gas management, hematocrit goals, electrolyte control, ultrafiltration techniques, and the use of deep hypothermic circulatory arrest (DHCA) are all integral aspects of a complex practice that forms the protocol at a given institution. Each of these can impact cerebral perfusion, but no standardization exists for any of these parameters. Therefore, understanding the consequence of altering a single aspect of bypass care is unclear, and demonstrating the optimal combination of bypass parameters is prohibitively difficult.

Due to the pressing need to improve neurocognitive outcome, and poor guidance afforded by evidence-based approaches to bypass management, effort and expense have been directed toward developing perioperative neuromonitoring strategies for children who require cardiac surgery and CPB. The monitoring technologies described in this chapter have been in routine use for more than a decade, but there is no universal consensus regarding their usefulness or validity, and there is no standard of care neuromonitoring practice for the patient with CHD. This chapter reviews cerebrovascular physiology and the impact of CPB on cerebral hemodynamics, available neuromonitoring modalities, and proposed strategies for improving neurodevelopmental outcomes after congenital heart surgery.

**KEY POINTS: MRI DIAGNOSED BRAIN INJURY IN NEONATAL CARDIAC SURGERY**

- Preoperative neurologic injuries occur in 20–40% of newborns with critical heart defects.
- After surgery, 35–75% of these patients will have a new brain injury.
- The most common brain lesion visible in the MRI of infants after congenital heart surgery is white matter injury, similar to periventricular leukomalacia seen in preterm infants.

**Cerebrovascular physiology during cardiac surgery**

Understanding cerebral perfusion and how it is affected by CPB is necessary to understand normal and abnormal neuromonitoring results during cardiac surgery. In health, cerebral perfusion regulation is known to be a finely tuned,
multilayered servo control of several homeostatic mechanisms, each acting independently with regard to stimulus and frequency, but in concert at the point of action: mediating cerebral vascular resistance. These mechanisms include neurovascular coupling (also known as metabolic autoregulation), CO$_2$ reactivity, pressure autoregulation, hypoxic vasodilatation, hypoglycemic vasodilatation, and the uneven action of systemic vasoconstrictors to cerebral relative to non-cerebral vasculature. Physiologic changes of the cerebral vasculature during bypass were largely defined by a series of studies performed in the 1980s and 1990s. Cerebral blood flow was measured using the Kety–Schmidt technique, and cerebral blood flow (CBF) velocity was measured with transcranial Doppler in both human infant and animal model studies. These efforts have highlighted the effects of extreme hypothermia and circulatory arrest on vascular tone, CBF and oxygen delivery and utilization within the brain.
Cooling and rewarming

During the cooling phase of CPB, CBF is reduced, and cerebral metabolism is reduced, presumably due to neurovascular coupling, which matches CBF to metabolism. However, during deep hypothermia, cerebral metabolism is exponentially reduced while CBF is reduced linearly with reduction in temperature (see Figure 11.3). This results in a state of “luxury perfusion” during hypothermia [27–30]. Shown another way, at normothermic bypass between 35.5°C and 37°C, the ratio of CBF (in mL/100g/min) to cerebral metabolic rate for oxygen consumption (CMRO₂, in mL/100g/min) is normal (20:1). At 30°C the ratio increases to 30:1, and at 18°C it increases to 75:1, indicating uncoupling of brain metabolism and vascular tone (see Figure 11.4). Based on the measured decrease of CMRO₂ in children during deep hypothermic bypass, Greeley et al. famously estimated a duration of ischemia that could be safely tolerated between 39 and 65 minutes [28]. When rewarmed after hypothermia in the absence of circulatory arrest, there is a return to normal CBF and metabolism with normal flow/metabolism coupling.

It is generally stated that cooling ablates pressure autoregulation as well as metabolic autoregulation. The two mechanisms are distinct processes that occur at distinct frequencies. Neurovascular coupling (metabolic autoregulation) is mediated by a neurovascular unit comprising an astrocyte bridge between neuronal synapses and penetrating arterioles. Neurovascular coupling is spatially specific and rapidly active, effecting vascular changes within 1 second of local neuronal activation [31]. By contrast, pressure autoregulation responds to sustained changes in cerebral perfusion pressure lasting 30 seconds or longer, and causes more global changes in CBF [32]. The conclusion that hypothermia also ablates pressure autoregulation comes from two independent investigations, one using transcranial Doppler, and the other using the Kety–Schmidt technique with xenon washout during infant bypass [28,30,33]. However, in both data sets the measurements of flow or flow velocity are taken at lower cerebral perfusion pressures than those taken at normothermia, and most of the hypothermic measurements are taken below the apparent limit of autoregulation evident in the normothermic plots. Therefore, it is not possible to tell if hypothermia or hypotension is the cause of impaired autoregulation. Further, measuring autoregulation with regression from intermittent measurements of CBF has limited granularity and has left the question of pressure autoregulation during profound hypothermia open for debate. This question may be resolved with newer metrics of dynamic autoregulation, which evaluate the pressure-vascular reactivity response at frequencies specific to pressure reactivity [34].

**pH-stat vs. alpha-stat blood gas management**

pH-stat management corrects blood gas values for temperature during CPB, which results in a higher arterial CO₂ tension during hypothermia than is achieved with
alpha-stat blood gas management. Obviously, regardless of the measurement technique used for determining the amount of CO\(_2\) in the blood, removing less CO\(_2\) or adding CO\(_2\) to the sweep gas with the oxygenator during bypass results in a higher arterial CO\(_2\) tension. CO\(_2\) diffuses freely across the blood–brain barrier, acidifying cerebrospinal fluid, which exerts a potent cerebral vasodilatory effect. The cerebrospinal fluid slowly returns to normal pH after exposure to high CO\(_2\) levels by increased activity of carbonic anhydrase in the choroid plexus, replacing reabsorbed acidic spinal fluid with spinal fluid having a higher concentration of bicarbonate buffer. Driving CBF changes by manipulation of arterial CO\(_2\) tension is therefore time-limited by the rate of spinal fluid absorption and production. Spinal fluid production is slower in infants than in adults, but in adults the entire spinal fluid volume is produced three to four times per day. Not surprisingly, then, animal models have shown that sustained changes in arterial CO\(_2\) tension cause CBF changes that last approximately 1 day [35,36]. In addition to increasing CBF, arterial hypercapnia shifts the oxyhemoglobin dissociation curve to the right, facilitating oxygen unloading [37]. Thus, in most pediatric centers, pH-stat (hypercapnia) strategy is favored for perceived neuroprotection.

In animal models of DHCA, neurologic outcome is improved when pH-stat is used. This has been more difficult to demonstrate in human infants, although a trend toward a lower death rate, fewer seizures, and greater hemodynamic stability has been observed [38]. Long-term neurologic follow-up at 4 years of age has not shown a difference between pH-stat or alpha-stat blood gas management, and this has only been studied retrospectively in a pediatric setting [37,39].

### Hemodilution and transfusion practices during CPB

Traditionally, profound anemia was used during deep hypothermic CPB to offset the effect of cooling on blood viscosity. This practice, rooted in theory, was challenged by demonstration of increased neurologic injury in a piglet model of hypothermic circulatory arrest using a target hematocrit of 30% when compared with a target of 20% [40]. More convincing was a randomized study of hematocrit goals at Boston Children’s Hospital. The combined data from two trials at Boston included the neurodevelopmental outcomes of 271 infants at 1 year of age. The Psychomotor Development Index increased linearly with hematocrit up to 23.5%. The Mental Development Index did not exhibit an association with hematocrit. The overall conclusion of this analysis was that although a hematocrit higher than 24% improved outcome, the effects of hemodilution vary according to age and other parameters of perfusion, especially pH management, precluding delineation of a universally optimal hematocrit [41].

### Temperature management

Hypothermia remains the cornerstone of brain protection for ischemic injury. Cerebral hyperthermia frequently develops after congenital heart surgery with CPB. The metabolic rate and oxygen consumption of the brain are raised during a period when oxygen delivery may be compromised due to hypotension. This places vulnerable watershed areas and partially injured brain tissue at risk for injury extension [42]. Bissonnette et al. measured temperatures in the jugular bulb, tympanic membrane, lower esophagus, and rectum during and after surgery in 15 infants, showing that the jugular bulb temperature continued to rise for at least 6 hours postoperatively [43]. The authors found that rectal temperature does not reflect cerebral temperature in the perioperative period. Other investigators further showed that nasopharyngeal and not tympanic temperature best reflects brain temperature [42]. However, Cottrell et al. were unable to show any association between neurocognitive performance and postoperative temperature in a cohort of 329 infants who underwent cardiac surgery [44].

In some patients, brain metabolism is not adequately suppressed during rapid cooling to deep hypothermic levels. In a study of infants undergoing cooling to 15°C, six of 17 had low jugular venous bulb saturation when this temperature was achieved (87 ± 6% vs. 98 ± 1% in subjects with apparently normal cooling), suggesting ongoing oxygen consumption that outstripped delivery of oxygen to the brain [45]. There is general concern that uneven or inefficient cooling of the brain may lead to neurologic deficits. Rapid cooling times have been associated in pilot studies with developmental delay and the rare complication of choreoathetosis [46,47]. There is little debate about the benefits of cooling during CPB, yet there is also insufficient data to suggest that any cooling strategy leads to better patient outcome [39].

### Glucose management

In the Boston circulatory arrest study, hyperglycemia was not associated with worse neurologic outcome and does not appear to be a risk factor for infants and children [48]. Intraoperative glucose concentrations were not related to developmental scores up to 8 years of age, but low...
glucose concentrations were associated with subclinical seizure activity [49]. In a study of 188 neonates and infants younger than 6 months undergoing surgery with CPB, mean intensive care unit (ICU) admission glucose was 328 mg/dL, maximum was 340 mg/dL, and 89% of patients had at least one value greater than 200 mg/dL. In that cohort, hyperglycemia was not associated with lower neurodevelopment scores at 1 year of age [50]. Tight glucose control is not indicated by evidentiary review in children who require CPB, and is likely to be harmful in this population [39].

**Circulatory arrest**

For infants who require reconstruction of the aortic arch, a bloodless field cannot be achieved with standard cannulation techniques. When DHCA is employed for this scenario, a profound cerebrovascular derangement occurs that persists into the rewarming and postoperative recovery periods. This cerebrovascular injury has been characterized by low CMRO$_2$ that fails to return to baseline values, low CBF (with a normal CBF:CMRO$_2$ ratio), and a distinctive transcranial Doppler flow velocity pattern showing absent or reversed flow during diastole (see Figure 11.5) [51–54]. These derangements have been shown to be reduced in incidence by the use of low-flow CPB instead of circulatory arrest, delayed rewarming, the use of pH-stat blood gas management during cooling, modified ultrafiltration, thromboxane A$_2$ antagonism, and the administration of nitric oxide donors [51,55–59]. Although these therapies mitigate the post-circulatory arrest physiologic derangement of the cerebral vasculature, there is no evidence that they change the incidence of periventricular leukomalacia, nor is it proven that these techniques improve the neurocognitive performance of patients with CHD.

**KEY POINTS: DEEP HYPOTHERMIC CIRCULATORY ARREST**

- Deep hypothermic circulatory arrest in infants is associated with a profound cerebrovascular disturbance characterized by low CMRO$_2$ and low CBF that is absent or reversed in diastole.
- This condition persists into the postoperative period.

**Selective cerebral perfusion**

Selective cerebral perfusion (also termed regional low-flow cerebral perfusion, antegrade cerebral perfusion or regional cerebral perfusion) is the surgical response to concerns that circulatory arrest causes neurologic injury. A variety of techniques achieve the same goal of delivering bypass flow to the cerebral vasculature while leaving a bloodless aortic arch for surgical repair. In one version of the technique, a polytetrafluoroethylene graft is sewn into the innominate artery and subsequently cannulated for bypass, in lieu of the traditional cannulation at the aortic root. When selective perfusion is desired, the great vessels are snared and flow is continued at a reduced rate, now entirely directed to the circle of Willis (see Figure 11.6). It seems evident that circulatory arrest and impaired neurovascular recovery after circulatory arrest would cause
neurologic injury, but there is no agreement that circulatory arrest should be replaced with either low-flow bypass, or newer techniques of selective antegrade cerebral perfusion.

For instance, neurocognitive testing of a 238-subject cohort at 4 years of age following surgery in infancy at the Children’s Hospital of Philadelphia showed that duration of hypothermic circulatory arrest was not associated with a poor performance in any category of the neurodevelopmental test [60]. Gaynor et al. argued with this result that non-modifiable factors such as genetic anomaly, socioeconomic status, maternal education, and gestational age were overwhelmingly responsible for poor results on neurocognitive testing, and that circulatory arrest is not a contributor to poor neurologic outcome. This result and interpretation contradict the most popular reading of studies related to the Boston circulatory arrest trial, which showed increased seizures and lower development scores in multiple functional domains at 1, 4, and 8 years of follow-up in subjects who underwent circulatory arrest as a randomized intervention [3,5,48,61,62]. With later testing in the teenage years of the same cohort, differences between arrest and non-arrest groups are less apparent [63]. Although the Boston circulatory arrest trial is one of the most widely studied and cited research efforts on the topic of neurologic injury and circulatory arrest, it is difficult to compare contemporary practice with the bypass strategy from 1990, which included deliberate hemodilution to a hematocrit of 20% [64].

More recently, the “Hearts and Minds” study performed in Auckland, New Zealand, and Melbourne, Australia, found that longer periods of circulatory arrest were associated with a significant increase in the severity of periventricular white matter injury (WMI) [20] (see Figure 11.7). In the Hearts and Minds study, many non-modifiable characteristics were more significantly associated with WMI than the use of circulatory arrest. These included the nature of the cardiac lesion and the brain maturity score. The presence of WMI was not associated with 2-year neurocognitive performance in that cohort.

Two trials comparing circulatory arrest with selective cerebral perfusion found no difference in neurocognitive outcomes at 1 year. Visconti et al. studied 29 subjects with HLHS who received either selective cerebral perfusion or circulatory arrest without randomization for the Norwood procedure [65]. Goldberg et al. studied 77 subjects with the same condition, randomized for the two bypass strategies [66]. Neither study showed significant improvements with the selective perfusion technique, but it has been argued that neurodevelopmental scores in both groups were lower than expected.

Another randomized trial of selective cerebral perfusion vs. circulatory arrest was done with 37 neonates requiring arch reconstruction. More than 70% of subjects in both groups of that study had a new MRI injury. White matter injury was the most common new lesion in both groups, but 33% of the subjects in the selective perfusion group had a deep embolic stroke on the side used for selective perfusion [67]. This high rate of an unusual neurologic injury is contrasted with a cohort of 57 neonates with high-risk lesions, all undergoing selective cerebral perfusion from Texas Children’s Hospital. In that observational cohort, a 40% incidence of new injury was seen, with WMI being the most common, and none had evidence of unilateral embolic load, despite a high flow rate during selective perfusion (56 ± 10 mL/kg/min). In the Texas cohort, duration of selective perfusion was not associated with poor neurocognitive outcome, but the duration of circulatory arrest was associated with a significant worsening in the cognitive domain at 1 year follow-up [7].

Selective cerebral perfusion and flow rates
Adding to the debate over whether to use hypothermic circulatory arrest or selective cerebral perfusion is the problem of choosing a flow rate when perfusing the circle of Willis directly. In the normal state of perfusion, the brain is protected from over- and under-perfusion specifically by the mechanism of pressure autoregulation. There is evidence that pressure autoregulation is entirely pressure-driven, and that cardiac output (or pump flow rates) is not relevant to cerebral perfusion as long as perfusion pressure is within the limits of autoregulation [68–70]. However, the ability of the cerebral vasculature to increase and decrease flow is at least conceptually dependent on a parallel vascular connection with the rest of the systemic circulation from which it can draw flow when vasodilating, and to which it can push flow when vasoconstricting. With the great vessels snared and flow directed to the carotid, there is an unknown narrowing of the range of flow rates that yield pressures acceptable for cerebral perfusion. Inconceivably wide ranges of selective perfusion flow rates have been published, from 10 to 100 mL/kg/min [71,72].

Experimental work in piglets has addressed this question. DeCampli, Myung et al., and Sasaki et al. independently studied similarly aged infant piglets with selective perfusion techniques at different flow rates.
By recording arterial blood pressure at the limb ipsilateral to the cannulation site, it was possible to see the relationship between flow rates and resultant pressure directed to the cerebral vasculature (see Figure 11.8). Published reports of neonates studied during selective cerebral perfusion have recorded the right radial arterial blood pressure during right innominate cannulation, which allows for the same relationship to be described in humans (see Figure 11.8) [15,72,76–79]. Although the piglet data suggests a safe range of flow rates between 20 and 30 mL/kg/min, examination of the human data clearly shows that the piglet data cannot be translated in this fashion. The human infant achieves a lower cerebral perfusion pressure for the same flow rates when compared with the piglet during selective perfusion. Further, the use of pH-stat blood gas management in the human infant increases the required flow rate, whereas pH-stat blood gas management in the piglet does not seem to change flow rate requirements during selective perfusion.

The translation of selective perfusion data from piglet to human would require accounting for differences in brain size (60 g piglet brain, 450 g human infant brain), brain development (the piglet is born ambulating with myelinated white matter, with different metabolic requirements and CBF), as well as the ratio of cerebral to collateral systemic circulation that occurs due to anatomic differences. Given the observed response to blood gas management changes shown in Figure 11.8, one can argue that the ratio of cerebral to non-cerebral perfusion in the human during selective perfusion is much higher than the piglet model of selective perfusion. The basis of this argument is that CO₂ tension changes in the blood affect cerebral vascular tone, but leave non-cerebral vascular tone relatively unchanged. If the piglet had a large percentage of CBF to total blood flow during selective perfusion, the pressure would drop with pH-stat management, as it does in human infants.

Cerebral blood flows during bypass have been measured in piglets and human infants under both alpha-stat and pH-stat blood gas management and are summarized in Table 11.1 to facilitate comparison of the human infant with the piglet model [30,75,80–84]. The piglet has a higher CBF/100 g of tissue, but pump flows are determined by

### Table 11.1 Human vs. neonatal piglet models of selective cerebral perfusion

<table>
<thead>
<tr>
<th>Study subject</th>
<th>Brain weight (g)</th>
<th>Body weight (kg)</th>
<th>PaCO₂ management</th>
<th>CBF/brain weight (mL/100g/min)</th>
<th>CBF/body weight (mL/kg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piglet</td>
<td>60</td>
<td>3</td>
<td>α-stat</td>
<td>25</td>
<td>5</td>
</tr>
<tr>
<td>Piglet</td>
<td>60</td>
<td>3</td>
<td>pH-stat</td>
<td>60</td>
<td>12</td>
</tr>
<tr>
<td>Human infant</td>
<td>450</td>
<td>3</td>
<td>α-stat</td>
<td>12</td>
<td>18</td>
</tr>
<tr>
<td>Human infant</td>
<td>450</td>
<td>3</td>
<td>pH-stat</td>
<td>20</td>
<td>30</td>
</tr>
</tbody>
</table>

CBF, cerebral blood flow. The translation of piglet studies of cerebral perfusion is best understood after comparing the relative mass of the piglet and human brain, the relative body mass of the piglet and human infant, and CBF expressed in standard units (mL/100g/min), and in units relevant to perfusion (mL/kg/min). The effect of blood gas management is also shown. The human brain under pH-stat management is predicted to require six times the pump flow rate of a piglet under α-stat management. The effect of non-cerebral tissue vasculature remains unknown.
body weight, not brain size. Therefore, the CBF rates/kg body weight are much smaller. These differences limit the applicability of piglet studies of selective perfusion to clinical practice.

An alternative approach has been to rely on neuromonitoring of individual patients to determine selective perfusion flow rates. The transcranial Doppler is used to determine flow velocities in the middle cerebral artery after cooling, but before selective perfusion. With initiation of selective perfusion, flows are gradually increased from zero until the flow velocities are equal to the pre-selective perfusion values [72]. This technique results in a wide inter-patient variability in flow rates, with a mean flow rate of $56 \pm 10$ mL/kg/min. Of 57 high-risk patients reported with this technique, 23 (40%) had a new MRI-detected brain lesion after surgery. Most lesions were WMI, and the lesions were evenly divided between ipsilateral and contralateral hemispheres with respect to the cannulation site. Non-randomized neurodevelopmental outcomes using the Bayley scales of infant development at 12 months yielded cognitive domains on a par with population norms, and language and motor domains 0.8 and 0.9 standard deviations (SDs) lower than population norms [7].

**KEY POINTS: SELECTIVE CEREBRAL PERFUSION**

- During selective perfusion, with the great vessels snared and flow directed to the carotid, there is an unknown narrowing of the range of flow rates that yield pressures acceptable for cerebral perfusion.
- Flow rates for selective perfusion have ranged from 10 to 100 mL/kg/min.
- A transcranial Doppler and near-infrared spectroscopy-guided flow protocol with mean $56 \pm 10$ mL/kg/min has been published, yielding a low rate of new MRI injury and good 12-month neurodevelopmental outcomes.

**Neurological monitoring during congenital heart surgery**

If a man will begin with certainties, he shall end in doubts: but if he will be content to begin with doubts, he shall end in certainties.

Francis Bacon, 1605 [85]

Empiricism, inductive reasoning, and the scientific method have converted medicine from mysticism to an evidence-based practice. The randomized controlled clinical trial is not new to medical science, but the modern ability to assimilate the vast catalog of medical data has been transformative [86]. The contemporary concept of evidence-based medicine by meta-analysis is a rigorous, methodical scoring of available evidence that provides a common platform for the standardization of practice [87]. Neuromonitoring has been reviewed with this matrix. In the case of all three neuromonitors presented in this chapter (electroencephalography, transcranial Doppler ultrasonography, and reflectance near-infrared spectroscopy), the final evidentiary scores were level III, i.e. no demonstrable benefit [39]. The antithesis of evidence-based practice includes two categories of offense: non-conformity to practices shown to be beneficial, and adherence to practices not shown to be beneficial. While no monitoring device has been shown by this evidentiary standard to be beneficial, the American Society of Anesthesiologists continues to recommend a standard, minimum acceptable intraoperative monitoring platform to include pulse oximetry, blood pressure and electrocardiography [88]. This breach of evidence-based practice is most pointed for the pulse oximeter, which is a mandatory intraoperative monitor despite failure of research to show any outcome benefit after randomization of nearly 23,000 subjects [89]. The universal refusal of practitioners to disbelieve the apparent benefit provided by pulse oximetry casts doubt on the ability of the randomized trial to demonstrate benefit for any monitoring modality [90]. For similar reasons, final conclusions in meta-analyses of intraoperative neuromonitoring, including those described hereafter in this chapter, are commonly upgraded in tone from “not indicated” to “may be considered,” despite the inability to support this conclusion with data [39,91].

**KEY POINTS: EVIDENCE-BASED MEDICINE AND PHYSIOLOGICAL MONITORING OUTCOME STUDIES**

- The pulse oximeter is a mandatory intraoperative monitor despite failure of research to show any outcome benefit after randomization of nearly 23,000 subjects.
- The universal refusal of practitioners to disbelieve the apparent benefit provided by pulse oximetry casts doubt on the ability of the randomized trial to demonstrate benefit for any monitoring modality.

**Electroencephalographic technologies**

The standard electroencephalogram (EEG) with two to 16 channels has been utilized in congenital heart surgery [92]. The EEG has a primary clinical purpose of detecting and diagnosing seizure activity. More recently, it has been used as a guide of anesthetic depth, and to document electrocerebral silence before circulatory arrest [93]. EEG is affected by several factors, including anesthetic agents, temperature, and CPB. Impracticalities associated with intraoperative EEG include electrical signal interference, complexity of placement, and interpretation. Newer devices using processed EEG technology are more...
Transcranial Doppler ultrasound

Transcranial Doppler ultrasonography is a sensitive, real-time monitor of CBF velocity and embolic events during congenital heart surgery. Currently available instruments utilize pulsed-wave ultrasound at 2 MHz frequency, which is range-gated, emits a power of 100 mW, and has a sample volume length up to 15 mm. Typically the middle cerebral artery is insonated during cardiac surgery, either across the fontanel or through the temporal bone window. Systolic, mean, and diastolic flow velocities are easily measured, as well as the pulsatility index, which is equal to the peak (systolic) velocity minus the end-diastolic velocity divided by the mean velocity [103].

The most challenging aspect of transcranial Doppler use is setting the proper angle and depth to reliably interrogate flow velocity in the middle cerebral artery. This is facilitated by the presence of pulsatile blood flow, and is therefore best done before initiation of bypass. Once located, small movements will require ongoing adjustments during the monitoring period to optimize the angle and depth of insonation. Cerebral vessels are not visualized by the ultrasound used, but are recognized by the patterns of flow velocity generated. When the temporal window is used, the bifurcation of the middle and anterior cerebral arteries is recognized in the Doppler signal by a maximal antegrade signal emanating from the middle cerebral artery and a similar magnitude retrograde signal emanating from the anterior cerebral artery. Insonation of the same vessel is necessary to effectively use the transcranial Doppler during surgery, and the use of the middle and anterior cerebral artery bifurcation allows the same region to be identified due to the simultaneous bi-directional flow signal (see Figure 11.9).

Transcranial Doppler ultrasonography has been used extensively in pediatric cardiac surgical research to examine the cerebral physiologic responses to CPB, hypothermia, low-flow bypass, regional perfusion techniques and circulatory arrest. These studies are discussed in the section on “cerebrovascular physiology during cardiac surgery.” Transcranial Doppler monitoring can also be used to detect cerebral emboli, but the embolic load detected with this method has not been shown to correlate with acute postoperative neurologic deficits [104]. In addition, transcranial Doppler monitoring can be used to detect cannula malposition at either the superior vena cava or aortic sites, which is seen as an abrupt decrement in the middle cerebral artery flow velocity [105].

Monitors of cerebral oxygenation

Jugular venous bulb oximetry

Jugular bulb venous oximetry (SjvO2) has been used in children with CHD since the late 1980s. It is considered the gold standard for the assessment of global cerebral oxygenation, against which reflectance near-infrared spectroscopy monitors were validated. The catheter can be placed in the jugular bulb by retrograde cannulation of the right internal jugular vein, with or without fluoroscopic confirmation of catheter tip placement [83]. Alternatively, the superior vena cava can be cannulated in the surgical field after exposure [106]. SjvO2 is conceptually a measure of the ratio of oxygen delivery to consumption in the brain. During bypass in adults, low SjvO2 has been associated with low cerebral perfusion pressure and low PaCO2; high SjvO2 is associated with low temperature [107]. The limited data available for SjvO2 monitoring are not likely to be augmented in the future because the method is invasive and time-consuming when compared with reflectance near-infrared spectroscopy, which renders a physiologically similar variable.

Near-infrared spectroscopy

In 1977, Frans Jobsis envisioned a neuromonitor for critically ill preterm neonates based on reflectance near-infrared spectroscopy [108]. The “NIRO-SCOPE” he developed was first used in 1985, in the neonatal intensive care unit at Duke University and led to the claim that [109]:

For effective measurement of cerebral oxygen sufficiency in a sick newborn, an instrument should be non-invasive, be adaptable at the bedside, not interfere with patient care, and give continuous rapid information. The signals should
directly assess brain oxygen delivery and utilization and be sensitive to small changes. The NIROS-SCOPE appears to fulfill these basic requirements.

The NIRO-SCOPE was never FDA-approved for use in the United States, and cerebral oximetry in general has gained little traction in the neonatal ICU market. However, the technology developed by Jobsis and his colleagues has evolved into four US FDA-approved devices: INVOS™ (Covidien, Mansfield MA, USA), Fore-Sight® (CASMED®, CAS Medical Systems, Inc., Branford, CT USA), Equanox™ (Nonin Medical Inc., Plymouth, Minnesota, USA), and CerOx™ (Ornim Inc., Dedham, MA, USA), of which all but the CerOx are currently also approved for pediatric use. In addition, the NIRO®-200NX (Hamamatsu Photonics, Hamamatsu City, Japan) is available in Japan and many parts of Europe.

Cerebral oximeters include a sensor placed on the forehead below the hairline (see Figure 11.10). Near-infrared light penetrates human tissues, including bone, without ionization. Light in this spectrum is, however, absorbed by specific biologic chromophores (i.e., hemoglobin and cytochrome oxidase $\text{AA}_3$) with molar absorptivity that is dependent on the state of oxidation of the chromophore (see Figure 11.11).
When near-infrared light, whether originating from a laser or a light-emitting diode, is applied to the human forehead, it passes through tissue in all directions, refracting off various tissue interfaces such that a portion of the light returns to the surface where it can be detected. In the laboratory, using a cuvette and spectrophotometer, the Beer–Lambert equation is used to calculate the concentration of a single chromophore based on absorbance ($A$). Absorbance is calculated from the relative intensities of recovered ($I$) and incident ($I_0$) light passing through a cuvette in a spectrophotometer:

$$ A = -\log \left( \frac{I}{I_0} \right) = \varepsilon \lambda LC $$

where $A$ is absorbance, $\varepsilon \lambda$ is the molar absorptivity of the chromophore at the specified wavelength of light, $L$ is the path length of light, and $C$ is the concentration of the chromophore in the cuvette. Naturally, hemoglobin does
Regional cerebral oximetry is thought to describe the oxygen saturation of frontal cortical blood that is 70% venous, 5% capillary, and 25% arterial. Thus, cerebral oximetry is venous-weighted, but with some arterial contribution making it consistently higher than, but trending with, jugular venous oximetry [110–112]. In piglets during CPB including hypothermic circulatory arrest, the correlation between jugular venous oximetry and cerebral oximetry was strong (r = 0.91) [113]. Clinical replication of this data was significant, albeit less robust [112,114,115]. Critics of cerebral oximetry have not challenged the evidence that cortical oxygenation can be measured with reflectance near-infrared spectroscopy. Rather, the relevance to outcome, potential to misguide management, and justification of cost have been questions raised by evidentiary review [39]. Some highlights of the numerous observational studies showing an association between low cerebral oximetry and neurologic injury or neurocognitive outcome are discussed below.

A prospective study of 250 children with EEG, transcranial Doppler and cerebral oximetry monitoring during cardiac surgery showed that cortical desaturation (cerebral oximetry reductions of 20% from baseline) was the most common monitoring event. Postoperative neurologic abnormalities, including seizures, speech, movement, and visual disturbances, occurred in 26% of subjects with neuromonitoring abnormalities that were not treated. By comparison, neurologic sequelae were observed in only 6% of subjects with monitoring events that were treated, and 7% of subjects with no monitoring abnormalities [92]. Pre-and post-Norwood procedure brain MRI data from 22 subjects showed an association between new lesions and prolonged cortical desaturation [18]. Another cohort of 53 neonates with diverse congenital heart lesions showed an association between cortical desaturation and new brain lesions detected by MRI [116]. Using a mixed outcome metric combining length of ICU stay, need for extracorporeal membrane oxygenation (ECMO), and death, an association was found between 48-hour mean cerebral oximetry measurements and poor outcome in 50 neonates after Norwood for HLHS [117].

Monitoring and supporting cortical oxygenation during cardiac surgery are conceptually similar to “goal-directed therapy,” used for shock management in the ICU [118,119]. Recognition of cortical desaturation promotes interventions that increase oxygen delivery, so cerebral oximetry monitoring acts as a unidirectional influence on bypass practices toward higher hematocrit, higher flow rates, higher cerebral perfusion pressure, higher arterial carbon dioxide tension (pH-stat management), and the use of selective perfusion techniques [90]. Table 11.2 shows abnormalities associated with cortical desaturations and interventions performed at Texas Children’s Hospital for cortical desaturation events.

**Longer-term neurodevelopmental testing outcomes after congenital heart surgery**

The preceding discussion has focused on cerebrovascular physiology and neuromonitoring methods, and acute or short-term neurological injury and outcomes. A number of longer-term studies, e.g. 12 months to 16 years, have been published in the CHD population. These data are mostly generated from single-center cohorts of neonates and young infants studied prospectively after complex congenital heart surgery. There are several recent multicenter or combined studies that provide new data. These cohorts provide important insights into risk factors for the lower neurodevelopmental scores observed in 30–50% of neonates undergoing cardiac surgery in recent years, as they reach school age and beyond. The neurodevelopmental characteristics of this population often include deficits in cognitive, memory, language, fine-motor, behavior, attention, and executive functioning domains, with a neurodevelopmental signature similar to that observed in former preterm infants [120]. Gross neurological deficits such as hemiparesis, choreoathetosis, and profound developmental delay are observed infrequently in the modern era [121,122].

**Boston Circulatory Arrest Study**

The Boston Circulatory Arrest Study (BCAS) is a landmark study initiated in the late 1980s that has set the standard for study of long-term neurodevelopment in a substantial cohort from a single center, with detailed neuropsychiatric testing and MRI brain imaging now reported in 16-year-olds in the study. A total of 170 neonatal dextro-transposition of the great arteries (D-TGA) patients undergoing the arterial switch operation from 1988 to 1992 were enrolled and randomized to DHCA or low-flow CPB (50 mL/kg/min) as the predominant strategy. Alpha-stat management was used and hematocrits were maintained at about 20%. The main immediate postoperative findings were a higher risk of clinical seizures (odds ratio 11.4), EEG seizures (odds ratio 2.5), longer recovery time to EEG reappearance, and higher creatine kinase-brain isoform levels [48]. A total of 155 of these infants were tested at age 12 months with the Bayley Scales of Infant Development-I (Bayley-I), with Mental Development Index (MDI) 105.1 ± 15.0 (normal 100, SD ± 15), and Psychomotor Development Index 95.1 ± 15.5. Use of DHCA was associated with a 6.5-point deficit on the MDI, and...
Table 11.2 Causes and treatments of cerebral cortical oxygen desaturation used at Texas Children’s Hospital

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Principle</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low cerebral perfusion pressure</td>
<td>The brain is perfused by pressure, not cardiac output.</td>
<td>During CPB: increase flow rate and maintain afterload reduction. Vasopressor only if excessive vasoplegia is suspected. Check SVC and aortic cannulae. Off CPB: administer volume judiciously with monitoring of atrial filling pressures. Inotropic support to improve stroke volume. Pacing for bradycardia. Vasopressors when excessive vasoplegia is suspected, and judiciously when volume is not tolerated and/or arrhythmia precludes beta-agonist therapy.</td>
</tr>
<tr>
<td>Anemia</td>
<td>Low oxygen-carrying capacity increases vulnerability to watershed white matter injury. The infant heart has low tolerance for the volume administration of transfusion immediately after bypass.</td>
<td>Avoid excessive hemodilution during hypothermia, typically 30–35%. Blood transfusion and hemofiltration during CPB to a hematocrit greater than 40% at separation. Higher hematocrit at separation allows for a volume-neutral exchange transfusion of platelets if needed.</td>
</tr>
<tr>
<td>Fever</td>
<td>High brain temperatures increase CMRO$_2$. High global O$_2$ extraction yields low mixed venous oxygen saturations, affecting arterial saturation in infants with mixing lesions.</td>
<td>Fevers are treated with antipyretics. Cooling is easily controlled on CPB. After separation and in the ICU, cooling can be accomplished to normothermia when needed with adequate sedation.</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>Arterial hypoxia in the infant with a mixing lesion must be addressed systematically. Reflex administration of oxygen in this setting can result in systemic hypoperfusion.</td>
<td>Lung ventilation and perfusion: tracheal suction, recruitment maneuvers. Pulmonary to systemic flow ratio: evaluate for shunt occlusion, pulmonary vascular tone elevation.</td>
</tr>
<tr>
<td>Mixed venous desaturation</td>
<td>Infants with mixing lesions are especially vulnerable to decrements of mixed venous oxygen content. Systemic vascular tone is the most common cause. Excessive work of breathing, agitation, shivering, and fever can contribute to low mixed venous saturation.</td>
<td>Mixed venous desaturation: see below</td>
</tr>
<tr>
<td>Hypocarbia</td>
<td>Arterial CO$_2$ diffuses freely into the CSF while soluble buffers do not. Cerebral blood flow is increased by acidic CSF (increased CO$_2$) and decreased by basic CSF (decreased CO$_2$). CSF buffering over several hours compensates acute changes in cerebral blood flow caused by arterial CO$_2$ tension.</td>
<td>Alpha blockade is used for infants during CPB. Afterload reduction with milrinone, nipride, or ACE-inhibitors are a preferred first-line therapy after separation from CPB. Intubation, sedation, or paralysis may be necessary in the ICU depending on the acuity. Pressure support trials causing low mixed-venous oxygen saturation and cortical desaturation should be terminated. Whether pH-stat or α-stat methods of measuring arterial CO$_2$ tension are used, low cerebral blood flow can be mitigated during CPB by permissive hypercapnia.</td>
</tr>
</tbody>
</table>

CPB, cardiopulmonary bypass; SVC, superior vena cava; CMRO$_2$, cerebral metabolic rate for oxygen consumption; ACE, angiotensin-converting enzyme; CSF, cerebrospinal fluid.

PDI was inversely proportional to the duration of DHCA [123]. EEG seizures were associated with lower PDI scores. At age 8 years, when multiple domains are testable, the 155 returning subjects had overall scores on the Wechsler Intelligence Scale for Children-III as follows: full scale IQ, $97.1 \pm 15.3$; performance IQ, $94.9 \pm 14.3$; and verbal IQ, $99.8 \pm 16.6$. Presence of a ventricular septal defect (VSD) was associated with lower verbal IQ scores. Academic achievement scores were generally in the normal range, although 37% were receiving remedial academic services and 10% had repeated a grade [5]. Performance on these tests was decreased when DHCA duration was > 41 minutes (95% lower confidence limit, 32 minutes). The cohort as a whole was below expectations in terms of academic achievement, fine-motor function, visual-spatial skills, working memory, attention, and higher-order language skills. Of these subjects, 139 returned at age 16 years for further neuropsychological testing and brain MRI [63]; 65% of these adolescents utilized some form of specialized educational services, and most scores of academic achievement, memory, executive functions, visual-spatial skills, attention, and social cognition tests were all below reference population norms, mostly in the mid-90th percentile, with no association with DHCA vs. low-flow bypass group. Multivariable analysis revealed associations of parental IQ, DHCA duration, and EEG...
seizures with one or more neuropsychiatric outcomes. Structural MRI abnormalities, mostly evidence of remote ischemic hemorrhage, were present in 33% of the 111 subjects scanned. On quantitative MRI imaging, the arterial switch operation group as a whole demonstrated reduced fractional anisotropy in bilateral cerebral hemispheric, brainstem and cerebellar white matter, signifying impaired microstructural development. Shorter cooling duration, higher nadir temperature, longer total ICU length of stay, and need for subsequent operations were all associated with impaired white matter development [124].

The wealth of information gleaned from the BCAS data set the standard for all subsequent single-center studies. The uniform patient group (all D-TGA, no genetic abnormalities) receiving a single corrective surgery is important for minimizing subsequent confounders. The prospective, randomized controlled intervention design, EEG, MRI, and careful serial neurodevelopmental outcomes in a large group with high follow-up rate are unparalleled thus far in subsequent studies. BCAS also raises the issue that bypass management (i.e., alpha-stat management, rapid cooling, prolonged DHCA, hematocrit 20%) has changed significantly in many centers since the cases were done, and the long-term findings may not be the same with contemporary approaches. The infant outcome tests (e.g., Bayley Scales of Infant Development) have undergone revision and are now in their third version; there is no reliable method to translate results between versions.

**Children’s Hospital of Philadelphia Cohort**

Gaynor et al. enrolled 550 neonates and infants <6 months of age undergoing complex CHD surgery from 1998 to 2003 in a prospective study of apolipoprotein E (APOE) genotype and neurodevelopmental outcomes [125]. APOE is important in neuronal repair and previously had been demonstrated to affect outcome in Alzheimer’s disease. This cohort has yielded important information not only about APOE but also a number of other risk factors for impaired neurodevelopmental outcomes through school age. A variety of cardiac diagnoses were enrolled, including a substantial group of HLHS patients. In all 359 subjects tested at 1 year, MDI on the Bayley-II was 90 ± 15, and PDI was 78 ± 18 [126]. The APOE ε2 allele was associated with significantly lower MDI and PDI scores after multivariable adjustment. Other risk factors were lower birth weight, preoperative intubation, lower hematocrit on CPB, longer postoperative length of stay, additional CPB operations, and genetic syndromes including chromosome 22q11.2 deletion syndromes. The use of DHCA was not associated with lower Bayley-II scores. At age 4 years, neurodevelopmental outcomes were tested in 381 subjects using a battery of standard tests; overall scores in the eight domains tested were within normal ranges; however, more patients had severe impairment in at least one domain than the general population. Cardiac diagnosis was demonstrated to be associated with outcomes, with HLHS patients performing worse than TGA, tetralogy of Fallot, or VSD patients without chromosomal anomalies in unadjusted analyses; these differences were less apparent after multivariable adjustment. In a separate report, EEG seizures in the perioperative period, which occurred in 11% of the cohort, were associated with worse executive function and impaired social interactions [127]. In another report of 92 of these infants who underwent DHCA, with a median of 36 minutes (range 1–132), DHCA was not associated with worse neurodevelopmental outcomes compared with those infants who had not undergone DHCA [128]. Finally, younger gestational age in this cohort was associated with worse outcomes, with 39–40 weeks gestational age at birth performing better in multiple domains at age 4 years than those born at less than 39 weeks [129].

**Western Canadian Study**

The Western Canadian Complex Pediatric Therapies Follow-up Group started prospective data collection of neonates and infants <6 weeks of age undergoing complex cardiac surgery in 1996–99; this group has reported additional cohorts having surgery as late as 2003–06. A variety of cardiac diagnoses were enrolled, including a third with HLHS, and a third with d-TGA. Their initial report of 85 infants included 67 survivors assessed at age 18–24 months with the Bayley-II [130]. The entire cohort has mean MDI of 84 ± 17, and PDI of 80 ± 22; chromosome anomaly conferred a major risk factor, and was found in 10/67 patients, with mean MDI 67 ± 16, and PDI 61 ± 17. Twenty-two percent of the population had profound mental delay (MDI <70), and 30% profound motor delay (PDI <70). Associated factors in the multivariable analysis included duration of preoperative ventilation, chromosome anomaly, duration of DHCA and CPB, and low arterial pH and high serum lactate, all associated with significant delay on Bayley-II. This group also assessed 16 subjects with deletion of chromosome 22q11.2 (DiGeorge syndrome), matched for cardiac lesion, socioeconomic status, and year of operation, with 16 patients without 22q11.2 deletion [131]. The 22q11.2 deletion patients (six interrupted aortic arch, six truncus arteriosus, four tetralogy of Fallot) had lower MDI (66.1 ± 10.6 vs. 86.3 ± 14.6, P < 0.001), and PDI (55.5 ± 9.4 vs. 82.3 ± 14.3, P < 0.001). In a separate report of this cohort in 61 patients at age 5 years, full scale IQ (FSIQ) was 89 ± 20, verbal IQ was 90 ± 20, performance IQ was 90 ± 20, and visual-motor integration (VMI) was 87 ± 17 [132]. The MDI as assessed at 18–24 months strongly predicted the FSIQ at 5 years (r = 0.817).

The Western Canadian Group has also reported on a later cohort, with complex cardiac surgery <6 weeks of age from 2003 to 2006, associating sedative, anesthetic, and analgesic drug exposure and neurodevelopmental outcomes [133]. They calculated the cumulative dose during the first 6 weeks of life for volatile anesthetics, opioids, benzodiazepines, ketamine, and chloral hydrate. At age 18–24 months they administered Bayley-II or -III (Bayley III after July 2004), and adaptive behavior and
language were also assessed by parent questionnaire. Multivariable analysis with the drug exposure variables, as well as a number of patient and surgical variables, was performed, with primary outcome being significant mental or motor delay < 70 on the Bayley scales, vocabulary delay < 15th percentile, and adaptive behavior scores. In all, 135 subjects were enrolled in the study; 19 died, 16 had chromosomal anomalies, and five were lost to follow-up, leaving 95 with neurodevelopmental assessments. Forty-eight percent of patients were D-TGA having undergone arterial switch, 24% were HLHS patients, and the remainder were other two-ventricle complete repairs. The overall cohort had mental and motor scores below the population norms but within 1 SD of normals; 11% had mental delay and 7% motor delay (in the normal population this is 2.5%), while 31% had vocabulary delay (normal is 15%). All patients received volatile agents, benzodiazepines (median 16 days), and opioids (median 15 days); 73% received chloral hydrate, and 56% received ketamine. There was no association with anesthetic or sedative drug dose and profound delays. Increasing days of ventilation, older age at surgery, lowest PaO₂, use of DHCA, and lower maternal education were all associated with significant delays. In a follow-up of the same cohort at age 4 years undergoing a comprehensive battery of neuropsychological tests in multiple domains, number of days on chloral hydrate was associated with lower performance IQ, and cumulative dose of benzodiazepines with lower visual-motor integration scores [134]. This study is limited primarily by the fact that drug exposure was only calculated for the first 6 weeks of life.

**Hearts and Minds Study**

The Heart and Minds Study is a prospective longitudinal cohort study of infants < 8 weeks of age undergoing cardiac surgery with or without CPB between 2005 and 2008 in Australia and New Zealand [20]. Subjects had pre- and postoperative brain MRI, and there was data collection and 2-year neurodevelopmental outcome testing using the Bayley-III. About half of the patients were single-ventricle palliations, and half were complete two-ventricle repairs. The overall neurodevelopmental scores of the 122 subjects with follow-up at age 2 years were as follows: cognitive, 94 ± 15; language, 94 ± 16; motor, 97 ± 12. The primary aim of the study was to determine the association of WMI with patient and surgical characteristics, and neurodevelopmental outcome. There was no association of WMI with Bayley-III scores; however, structural brain immaturity on MRI was associated with lower neurodevelopment.

**Milwaukee cohort**

Hoffman et al. reported on a cohort of HLHS patients undergoing stage I palliation in 2002–05, and then neurodevelopmental assessment at age 4–5 years [135]. The primary aim of the study was to determine the association of perioperative regional cerebral oxygen saturation (rSO₂), measured by near-infrared spectroscopy, with neurodevelopmental outcomes. Of 51 patients entering the study, 21 had complete neurodevelopmental assessment (48% of survivors). The composite neurodevelopmental outcome of cognition, language, attention, and VMI was 97.6 ± 9.6, was within normal population ranges, and with low performance frequencies also not different from reference population ranges. Patients demonstrating low or abnormal VMI had lower rSO₂ (63.6 ± 8.1 vs. 67.8 ± 8.1, P = 0.026) in the first 48 postoperative hours. They also spent more time at rSO₂ < 55% and 45% levels than those with normal VMI. Peripheral oxygen saturation (SpO₂) was also lower in these patients; however, other physiological variables (mean arterial pressure, PaCO₂, SvO₂, central venous pressure, hemoglobin, blood gas parameters) were not different. The breakpoint for lower VMI score in the multivariate model was an rSO₂ of 55%.

**Texas Children’s Hospital cohort**

The Texas Children’s Hospital cohort of neonates undergoing complex cardiac surgery at less than 30 days of age between 2005 and 2011 has been the subject of several neurodevelopmental outcomes publications [7,16,136,137]. Of 93 subjects entering two separate prospective studies, 59 (71%) survivors underwent 12-month Bayley-III testing; 47% of these patients had HLHS. Cognitive score was 102.1 ± 13.3, language score was 87.8 ± 12.5, and motor score was 89.6 ± 14.1. The major findings in these reports after multivariable analyses were as follows:

- Longer duration of regional cerebral perfusion was not associated with lower Bayley-III scores, but longer DHCA was associated with lower scores.
- New postoperative MRI brain injury, longer ICU length of stay, lower preoperative rSO₂, and chromosome anomalies were associated with lower Bayley-III scores.
- Larger volatile anesthetic agent exposure was associated with lower cognitive scores.

**Single Ventricle Reconstruction Trial**

The Single Ventricle Reconstruction (SVR) Trial is a multicenter study of stage I palliation for HLHS randomizing surgery to systemic to pulmonary artery shunt vs. right ventricle to pulmonary artery shunt [138]. Operations were performed between 2005 and 2008 in 15 centers. Neurodevelopmental outcomes were assessed with the Bayley-II at a mean of 14.3 ± 1.1 months of age. In all, 314 patients were assessed at that time (86% of transplant-free survivors), and mean MDI was 89 ± 18, and PDI was 74 ± 19, both profoundly lower than reference population norms. Multivariable regression models determined that site of surgery, birth weight less than 2500 g, longer length of stage I hospitalization, and greater number of complications were associated with lower PDI scores. Lower MDI scores were associated with lower birth weight, genetic syndrome or other anomalies, lower maternal education level, longer days on ventilation, and greater number of complications.
complications. Intraoperative variable data collection was limited, but none of these variables (DHCA vs. regional cerebral perfusion, alpha-stat vs. pH-stat, hematocrit) were associated with Bayley-II outcomes.

International Cardiac Collaborative On Neurodevelopment (ICCON) Investigators Cohort

The ICON Investigators group was recently formed, and has pooled early neurodevelopmental outcomes results for complex neonatal and young infant cardiac surgery with operations occurring between 1996 and 2009 [139]. Data were analyzed from 23 institutions utilizing Bayley-II testing performed on patients aged 6–30 months. The mean age of assessment was 14.5 ± 3.7 months, and the overall scores for the 1,770 patients were MDI 88.2 ± 16.7 and PDI 77.6 ± 18.8. Important findings were that cardiac class IV (single-ventricle patients with aortic arch obstruction, e.g., HLHS) was significantly more common in the later years of the studies. In the multivariable analysis, patient factors were evaluated, and cardiac diagnosis (class IV), genetic anomaly, lower maternal education, male gender, and lower birth weight were all associated with lower scores. After this adjustment, mean Bayley-II scores did increase significantly over time, with mean MDI and PDI scores increasing by approximately 0.4 points/year over the 14 years represented in the study. Perioperative treatment factors and strategies were not evaluated.

The studies reviewed in this section give an emerging, if incomplete, picture of risk factors for the now very well established lower neurodevelopmental outcomes in infants undergoing congenital heart surgery. The many recent reports emphasize significantly lower testing scores during infancy in most all cohorts; there are fewer reports at age of school entry or later. These reports at older ages give a profile of the preschool or school-aged child with subtle impairment in a number of domains, including executive functioning, language, attention, fine-motor function, visual-motor integration, and reasoning. As noted earlier, this profile is not dissimilar to the premature neonate. Both groups have in common structural and microstructural brain immaturity and a propensity to brain injury, with WMI being the most common. Comparison of outcomes over time is difficult, but there appears to be a trend of improving early outcomes, albeit in a patient population increasingly skewed toward more complex single-ventricle lesions. Debate is ongoing about the proportion of risk accrued to non-modifiable (i.e., innate) patient factors vs. modifiable ones (i.e., CPB techniques, neurological monitoring, anesthetic and sedative techniques, and ICU strategies). The multivariable models all have significant limitations, and the majority explain only 20–40% of the variation in the neurodevelopmental outcome scores; only a few models explain > 50%. Further complicating the concepts of non-modifiable factors may be emerging strategies for fetal intervention, by both catheter and medical interventions, that could improve both the cardiac and cerebral abnormalities observed in neonates with CHD. Table 11.3 summarizes data from the cohorts reviewed earlier, and Table 11.4 presents the modifiable vs. non-modifiable risk factors published in the studies reviewed here, and lists possible strategies for intervention, where applicable.

Conclusions

Truth in medicine is an unattainable goal, and the art as described in books is far beneath the knowledge of an experienced and thoughtful physician.

Muhammad Ibn Zakariya Al-Razi, c. 900 BCE

The neurologic vulnerability of children with CHD has been well characterized. White matter lesions suggestive of impaired oxygen delivery to watershed regions of the brain are the most common perioperative-acquired injury seen on MRI. The neurodevelopmental abnormalities of children with CHD are often subtle disorders of intellect, attention, impulsivity and executive functioning, which impact the quality of life of survivors of critical heart disease in infancy. The principles of CBF and oxygen delivery are equally well characterized, but the strategies to optimize these parameters during CPB are a subject of vigorous debate. A summary of the advantages and disadvantages of the neuromonitoring modalities discussed in this chapter is given in Table 11.5.

Does a neuroprotective strategy during CPB improve outcome?

Scientific investigation has failed to delineate an evidence-based neuroprotective practice for many of the most basic aspects of care during cardiac surgery and CPB, including the use of circulatory arrest or selective perfusion, and whether to monitor the brain during and after CPB. The perspective presented in this chapter emphasizes the physiologic principles relevant to neuro-protection, which are often the only available rationale for decisions that have to be made for critically ill children with CHD.

Single-center studies of cerebral oximetry where goal-directed therapy with cerebral oximetry monitoring is either embraced or rejected cannot show the effect of these practice shifts for lack of a comparison group. Outcomes from the Texas Children’s Hospital for neonates requiring cardiac surgery have been studied for both MRI-detected injury and neurocognitive performance. The CPB strategy at Texas Children’s Hospital is highly standardized to the use of goal-directed oxygen delivery support and selective perfusion techniques guided by multimodal neuromonitoring, including both reflectance near-infrared spectroscopy and transcranial Doppler insonation [143]. The rates of new neurologic injuries after surgery with this practice compare favorably with published studies of similar outcome measures. A varied critical-lesion infant cohort, including HLHS, TGA, truncus arteriosus,
Table 11.3  Summary of major neurodevelopmental outcomes cohorts after complex infant cardiac surgery

<table>
<thead>
<tr>
<th>Cohort [references]</th>
<th>N</th>
<th>Single (S) or multi-center (M)</th>
<th>Years of surgery</th>
<th>Age at follow-up</th>
<th>ND outcomes</th>
<th>Major associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boston Circulatory Arrest Study [5,48, 63,123,124]</td>
<td>155</td>
<td>S</td>
<td>1988–92</td>
<td>1, 8, 16 years</td>
<td>MDI 105, PDI 95*, FSIQ 97, PIQ 95, VIQ 100; adolescents with most scores mid-90th percentile</td>
<td>Prolonged DHCA with outcomes at 1 and 4 years; parental IQ, DHCA duration, EEG seizures at 16 years APOE e2 allele; lower BW, preoperative intubation, lower CPB hematocrit, LOS, additional CPB operations, chromosome/genetic anomaly, EEG seizures, younger GA, cardiac diagnosis (HLHS); DHCA use not associated</td>
</tr>
<tr>
<td>Philadelphia APOE Study [125–129]</td>
<td>381</td>
<td>S</td>
<td>1998–2003</td>
<td>1, 4 years</td>
<td>MDI 90, PDI 78; 92–105 on eight domains at 4 years, mean 97</td>
<td></td>
</tr>
<tr>
<td>Western Canadian Outcomes Group I [130–132]</td>
<td>61</td>
<td>S</td>
<td>1996–99</td>
<td>18–24 months, 4–5 years</td>
<td>MDI 84, PDI 80; FSIQ 89, VIQ 90, PIQ 90, VMI 87</td>
<td>Chromosome anomaly, preoperative ventilation, duration of DHCA and CPB, acidosis, lactate</td>
</tr>
<tr>
<td>Western Canadian Outcomes Group II [133,134]</td>
<td>95</td>
<td>S</td>
<td>2003–06</td>
<td>18–24 months, 4–5 years</td>
<td>MDI 86, Cog 98; PDI 85, Motor 95</td>
<td>Days of ventilation, older age, low PaO2, use of DHCA, lower parental education; days of chloral hydrate, cumulative dose benzodiazepines</td>
</tr>
<tr>
<td>Milwaukee HLHS Cohort [135]</td>
<td>21</td>
<td>S</td>
<td>2002–05</td>
<td>4–5 years</td>
<td>Cognitive IQ 95, attention 107, language 95, VMI 93</td>
<td>Volatile anesthetic exposure, ICU LOS, chromosome anomaly, MRI brain injury, rSO2, SaO2, DHCA; longer RCP not associated</td>
</tr>
<tr>
<td>Texas Children's Hospital Cohort [7,16,136,137]</td>
<td>59</td>
<td>S</td>
<td>2005–11</td>
<td>12 months</td>
<td>Cog 102, Lang 88, Motor 90</td>
<td></td>
</tr>
<tr>
<td>International Cardiac Collaborative on Neurodevelopment [139]</td>
<td>1,770</td>
<td>M (23)</td>
<td>1996–2009</td>
<td>6–30 months</td>
<td>MDI 88, PDI 78</td>
<td>Later year of surgery, cardiac class, genetic anomaly, lower BW, parental education</td>
</tr>
</tbody>
</table>

*BCAS used Bayley-I.

MDI, Bayley Scales of Infant Development-II Mental Development Index; PDI, Bayley Scales of Infant Development-II Psychomotor Development Index; Cog, Lang, Motor, Bayley Scales of Infant Development-III cognitive, language, and motor composite scores. ICU, intensive care unit; LOS, length of stay; HLHS, hypoplastic left heart syndrome; MRI, magnetic resonance imaging; EEG, electroencephalogram; rSO2, regional cerebral oxygen saturation; BW, birth weight; GA, gestational age; VMI, visual-motor integration; FSIQ, full scale intelligence quotient; VIQ, verbal intelligence quotient; PIQ performance intelligence quotient; DHCA, deep hypothermic circulatory arrest; RCP, regional cerebral perfusion.
Table 11.4 Modifiable and non-modifiable published risk factors for lower neurodevelopmental outcome scores after infant congenital heart surgery

<table>
<thead>
<tr>
<th>Factor (example)</th>
<th>Potential interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-modifiable factors</strong></td>
<td></td>
</tr>
<tr>
<td>Cardiac diagnosis (HLHS)</td>
<td>??Fetal catheter intervention; maternal (O_2) administration</td>
</tr>
<tr>
<td>Genetic anomaly (22q11.2)</td>
<td></td>
</tr>
<tr>
<td>Parental education/SES</td>
<td></td>
</tr>
<tr>
<td>Birth weight</td>
<td></td>
</tr>
<tr>
<td>Prematurity</td>
<td></td>
</tr>
<tr>
<td>Brain immaturity</td>
<td>??Maternal progesterone [140,141]</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td><strong>Modifiable factors</strong></td>
<td></td>
</tr>
<tr>
<td>Use and duration of DHCA</td>
<td>Avoid/limit DHCA duration [5]</td>
</tr>
<tr>
<td>Use of RCP</td>
<td>Use RCP in lieu of DHCA [143]</td>
</tr>
<tr>
<td>CPB hematocrit</td>
<td>Maintain &gt; 24% [41]</td>
</tr>
<tr>
<td>Low (rSO_2)</td>
<td>Intervene &lt; 50%</td>
</tr>
<tr>
<td>MRI brain injury</td>
<td>Avoid/limit DHCA duration [20]</td>
</tr>
<tr>
<td>Elective delivery &lt; 39 weeks GA</td>
<td>Early extubation; minimize sedation [137]</td>
</tr>
<tr>
<td>ICU LOS</td>
<td>Benzodiazepines [142]</td>
</tr>
<tr>
<td>Seizures</td>
<td>Limit volatile anesthetic exposure, ??dexamethasone [137]</td>
</tr>
<tr>
<td>Anesthetic technique</td>
<td>Surgical, anesthetic, ICU strategies</td>
</tr>
<tr>
<td>Low cardiac output/acidosis/factate</td>
<td>Oxygen delivery strategies; early surgical intervention</td>
</tr>
<tr>
<td>Low (PaO_2)</td>
<td></td>
</tr>
</tbody>
</table>

Non-modifiable factors could potentially be modifiable; experimental interventions are listed. HLHS, hypoplastic left heart syndrome; 22q11.2, partial deletion chromosome 22; SES, socioeconomic status; DHCA, deep hypothermic circulatory arrest; RCP, regional cerebral perfusion; \(rSO_2\), regional cerebral oxygen saturation; MRI, magnetic resonance imaging; GA, gestational age; ICU, intensive care unit; LOS, length of stay.

Table 11.5 Practical advantages and disadvantages of specific neuromonitoring modalities

<table>
<thead>
<tr>
<th>Monitor</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electroencephalograph</td>
<td>Detects subclinical seizures and confirms electrical silence during deep hypothermia</td>
<td>Requires expertise for interpretation; cumbersome array of electrodes</td>
</tr>
<tr>
<td>Transcranial Doppler</td>
<td>Allows for assessment of cerebral blood flow (velocity) during critical stages of cardiopulmonary bypass, especially selective perfusion</td>
<td>Technically challenging; flow velocities are dependent on the angle of insonation, which can be difficult to stabilize</td>
</tr>
<tr>
<td>Jugular venous oximetry</td>
<td>Gold standard measurement of cerebral venous oxygen content</td>
<td>Requires expertise to place the catheter in the jugular bulb; invasive to the cephalad venous drainage system in pre-Glenn patients</td>
</tr>
<tr>
<td>Near-infrared spectroscopy (NIRS)</td>
<td>Non-invasive measure of cortical blood oxygenation; technically easy to apply with a stable signal. Most widely used and familiar neuromonitor in the cardiac patient</td>
<td>Practical limitations are rare; disposable sensors are costly. Most centers who do not use reflectance NIRS do so for lack of level III outcome evidence</td>
</tr>
</tbody>
</table>

and interrupted aortic arch, demonstrated a 36% new MRI injury rate, with only 16% showing new WMI (see Figure 11.1 for comparison data) [15]. For the highest-risk neonates requiring arch reconstruction, duration of CPB and duration of selective perfusion were both free from association with low 12-month developmental score in any of the three domains tested: cognitive, motor, and language. The duration of circulatory arrest was, however, significantly associated with decreased cognitive performance at 12 months [7]. Thus, the goal-directed strategy, utilizing neuromonitoring, is a safe option for the management of CPB in neonates, but has not been shown to be superior to either circulatory arrest or non-monitored management in a randomized setting.

Selected References
A full reference list for this chapter is available at: http://www.wiley.com/go/andropoulos/congenitalheart


CHAPTER 12

Transesophageal Echocardiography in Congenital Heart Disease

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Introduction

To date, most institutions use a combination of imaging modalities, including echocardiography, cardiac catheterization and angiography, computed tomography (CT), and magnetic resonance imaging (MRI), for the comprehensive diagnostic evaluation of patients with congenital heart disease (CHD). Transesophageal echocardiography (TEE) has been a rapidly evolving field and has become a critically important cardiovascular imaging modality.

Since the introduction of TEE to the intraoperative setting in the late 1980s, its utility as a diagnostic and monitoring tool has been demonstrated in adult patients during cardiac and non-cardiac surgery. Until the early 1990s, intraoperative TEE in infants and small children was not feasible, as TEE probes of a suitable size were unavailable. Advances in ultrasound technology, specifically the miniaturization of imaging probes, have since permitted the safe use of TEE in this patient group.

TEE is currently considered by many cardiac centers to be the standard of care for assessing the adequacy of surgical interventions in children and adults with CHD. The imaging approach can immediately detect suboptimal surgical results, thus probably improving clinical outcomes by avoiding subsequent reoperations and reducing overall morbidity, mortality, and costs. The use of TEE in environments such as the cardiac catheterization laboratory, electrophysiology suite, and intensive care unit (ICU) also significantly facilitates the management of patients with CHD.

This chapter focuses on TEE for monitoring and assessment in CHD, highlighting its many benefits and roles in clinical practice. The intraoperative use is emphasized, as it represents the most common application of the technology in this patient population.

Indications for TEE in CHD

Echocardiography is the preferred imaging modality for the initial diagnostic assessment and follow-up of patients with CHD. Transthoracic echocardiography (TTE) provides excellent definition of cardiovascular anatomy in most patients. In fact, the exceptionally high resolution of TTE imaging in infants and young children with CHD is often sufficient to plan medical and surgical management.

Despite the merits of TTE, technical limitations yield suboptimal images in patients with poor windows caused by obesity, mechanical ventilation, and prior or recent...
cardiac surgery. TEE overcomes many of these limitations and can be extremely helpful when other imaging approaches, including TTE, provide insufficient information or where important diagnostic questions remain. The portability of TEE allows it to be performed in various settings. TEE in the patient with CHD is often performed as an adjunct to other diagnostic studies and as such should complement, but not substitute for, a complete TTE examination.

Several professional societies in North America and other countries have proposed when the use of TEE may be appropriate [1–4]. Specific indications for using TEE in the pediatric patient with CHD were addressed in guidelines by a task force of the Pediatric Council of the American Society of Echocardiography (ASE) and published in 2005 [5]. Three major categories for performing TEE in these patients were described: diagnostic assessment; perioperative evaluation; and related to percutaneous interventions (Box 12.1).

**Box 12.1: Indications for transesophageal echocardiography (TEE) in the patient with congenital heart disease (CHD)**

**Diagnostic indications**
- Patient with suspected CHD and non-diagnostic TTE
- Presence of PFO and direction of shunting as possible etiology for stroke
- Evaluation of intra- or extracardiac baffles following the Fontan, Senning, or Mustard procedure
- PFO evaluation with agitated saline contrast to determine possible right-to-left shunt, prior to transvenous pacemaker
- Aortic dissection (Marfan syndrome)
- Intracardiac evaluation for vegetation or suspected abscess
- Evaluation for intracardiac thrombus prior to cardioversion for atrial flutter/fibrillation
- Pericardial effusion or cardiac function evaluation and monitoring postoperative patient with open sternum or poor acoustic windows
- Evaluating status of prosthetic valve

**Perioperative indications**
- Immediate preoperative definition of cardiac anatomy and function
- Postoperative surgical results and function

**TEE-guided interventions**
- Guidance for placement of ASD or VSD occlusion device
- Guidance for blade or balloon atrial septostomy
- Catheter tip placement for valve perforation and dilation in catheterization laboratory
- Guidance during radiofrequency ablation procedure
- Results of minimally invasive surgical incision or video-assisted cardiac procedure

ASD, atrial septal defect; PFO, patent foramen ovale; TTE, transthoracic echocardiography; VSD, ventricular septal defect.

Outpatient TEE is used routinely as a diagnostic tool in many centers that care for adult patients with cardiovascular disease, including CHD, because transthoracic imaging becomes more challenging and less revealing as patients reach adulthood [6]. TEE plays an important role in this setting, as congenital anomalies may be highly variable in presentation. The benefits of TEE include the detailed evaluation of primary structural malformations, secondary compensatory cardiovascular changes, associated complications, and functional and hemodynamic consequences. The proximity of the imaging probe to the back of the heart provides optimal visualization of posterior cardiovascular structures. Overall, TEE is superior to TTE in the diagnosis of specific pathologies involving the aorta (Ao) and left atrial appendage (LAA), and in the evaluation of prosthetic heart valves, native valve masses, and complications resulting from endocarditis, including vegetations, abscesses, and fistula [7]. It is the imaging approach of choice to exclude thrombus prior to performing elective cardioversion in most patients with atrial rhythm disturbances. TEE is also useful in the evaluation of a potential cardiac source of embolism such as a patent foramen ovale (PFO) [8]. The modality can also enhance the assessment of intra- or extracardiac baffles in patients who have undergone Fontan, Senning, or Mustard procedures [9].

Intraoperative evaluation represents the most frequent application of TEE in CHD. Indications in both adults and children with CHD can be summarized as follows:
- All open-heart and thoracic aortic surgical procedures
- Surgical repair of most congenital heart lesions that require cardiopulmonary bypass (CPB)
- Surgery when significant residual abnormalities, such as outflow tract obstruction, valve regurgitation or stenosis, or intracardiac communications may occur.

Transesophageal echocardiography also provides significant benefits in patients with CHD undergoing cardiac catheterization procedures such as device closure of intracardiac communications (atrial or ventricular septal defects [ASDs or VSDs]), balloon valvuloplasty, perforation of the atrial venticle, atrial septostomy, and many other interventions [10–13]. Likewise, this imaging approach has been shown to be extremely useful during electrophysiologic procedures by providing guidance during catheter placement and assisting with ablation therapies [14,15]. In these various settings, TEE can offer valuable information that facilitates planning, refinement, and, upon completion, real-time assessment of the interventions.

Despite the considerable merits of TEE, it has inherent limitations, including the following:
- Imaging constraints within the gastrointestinal tract, resulting in suboptimal evaluation of structures or Doppler angles of interrogation
- Reduced far field imaging of anterior structures
- Semi-invasive nature of the procedure, often requiring sedation or general anesthesia, with associated risks
- Suboptimal examination conditions related to patient or environmental factors, such as limited time to perform
a comprehensive study, ambient lighting, and electrocautery interference.

**KEY POINTS: INDICATIONS FOR TEE**

- TTE provides adequate characterization of congenital cardiovascular malformations in most cases, particularly in children.
- TEE overcomes many of the limitations of TTE imaging, including suboptimal windows caused by obesity, mechanical ventilation, and prior or recent cardiac surgery.
- The main indications for TEE can be categorized into diagnostic assessment, perioperative evaluation, and related to percutaneous interventions.
- TEE in the patient with CHD should complement, but not substitute, a complete TTE examination.
- Perioperative use represents the most common application of TEE in the patient with CHD.

**Contraindications to TEE**

Prior to using transesophageal imaging, indications should be considered, contraindications excluded, informed consent obtained, and a complete review of relevant clinical information, including available echocardiographic studies and other diagnostic data, performed. Decision-making regarding the need for TEE should be undertaken judiciously in every patient, given the semi-invasive procedure with associated potential risks. In any clinical situation for which safety concerns exist, alternate imaging modalities should be entertained.

General contraindications to TEE include esophageal pathology, severe respiratory decompensation, or inadequate control of the airway (Box 12.2) [5,7]. Careful assessment of the risk–benefit ratio for TEE is warranted in patients with cervical spine injury or deformity and those with severe coagulopathy. In the presence of a gastrostomy feeding tube, transgastric examination is often deferred. Although the timing for when instrumentation of the esophagus can be performed safely following esophageal surgery has not been established, anecdotally, many children have undergone TEE imaging several months or years later without notable ill effects.

**Box 12.2: Contraindications to transesophageal echocardiography**

**Absolute**
- Unrepaired tracheoesophageal fistula
- Esophageal obstruction or stricture
- Perforated hollow viscus
- Active gastric or esophageal bleeding
- Poor airway control
- Severe respiratory depression
- Uncooperative, unsedated patient

**Relative**
- History of prior esophageal surgery
- Esophageal varices or diverticulum
- Vascular ring, aortic arch anomaly ± airway compromise
- Oropharyngeal pathology
- Severe coagulopathy
- Cervical spine injury or anomaly

Reproduced from, Ayres NA, Miller-Hance W, Fyfe DA et al. Indications and guidelines for performance of transesophageal echocardiography in the patient with pediatric acquired or congenital heart disease: report from the task force of the Pediatric Council of the American Society of Echocardiography. / Am Soc Echocardiogr 2005;18:91-98 (Table 2, p 94), with permission from Elsevier.

**TEE hardware**

The use of echocardiography requires knowledge of the science of ultrasound and the many important principles involved. The application of TEE assumes a thorough understanding of the instrumentation necessary to perform the examination. These aspects of echocardiography and TEE practice cannot be addressed in this chapter, even in abbreviated form; the interested reader is referred to detailed resources on the subject [16–21].

**Echocardiographic system**

Ultrasound machines suitable for echocardiography incorporate multiple modalities for image and signal processing during interrogation of the heart and vasculature. Modern systems integrate components such as a high-resolution display, a console with hard keys, connection ports for transducers, ports for physiologic monitors (e.g., electrocardiogram or ECG), and a computer with software for processing data and network ports.

Controls and their layout on the machine vary with each manufacturer; nonetheless, some common features among systems merit a basic understanding of their function. Manipulation of various knobs allow for adjustment in image quality, activation of modes, recording of images, and other functionalities. An understanding of how the machine operates is obviously essential for acquiring images of diagnostic quality. A discussion of these important aspects of echocardiography can be found in print [19,21] or in electronic resources.
TEE imaging probes

Several TEE probes are commercially available for clinical use (Table 12.1). In general, devices are not interchangeable among different echocardiographic systems and may not even be compatible between machines across the same platform. The ability to use a TEE probe in a particular system requires not only appropriate hardware compatibility but also specific software able to interface the imaging device with the echocardiography machine.

Evolution of transducer technology has put into practice TEE probes that have higher resolution than original devices, enhanced image plane options, and additional modes to better assess the cardiovascular system. These advances imply major improvements in our ability to undertake comprehensive evaluation of complex disease.

Early monoplane (single plane) TEE probes allowed for imaging only in the transverse orientation or horizontal plane (0°) [22]. Biplane probes incorporated a second scanning crystal, enabling, in addition, the longitudinal orientation or vertical plane imaging (90°), thereby providing information in planes perpendicular to each other (orthogonal planes) [23–27]. The introduction of multiplane (omniplane) probes permitted interrogation of cardiovascular anatomy in any plane between 0° and 180° [28–31]. These flexible devices all contain phase-arrayed transducers that produce “pie-shaped” or sector images. Monoplane and biplane devices have largely been replaced by sophisticated multipane probes offering a number of imaging planes to visualize most cardiac structures (Figure 12.1).

Recently, three-dimensional (3D) volume TEE scanning has become available using a specialized matrix-array probe (3D TEE) to display a selected volume of the heart as a real-time 3D dataset [32]. This information can also be manipulated in real-time to display anatomy from any perspective, including the surgical orientation [33,34]. This new advance replaces previously available 3D technology, which relied on offline reconstruction of sequentially acquired two-dimensional (2D) image planes, thus limiting its use in the operating room.

Device selection

Unlike the almost “one size fits all” nature of selecting an adult TEE probe, choosing among available TEE devices adds another layer of complexity and sometimes even inconvenience to imaging of pediatric patients (Figure 12.2). Selection of an appropriate probe in the pediatric age group is guided mainly by two parameters: weight of the patient and size of the probe (Table 12.2).

Multiplane imaging using an adult-sized TEE probe is preferred in older children. Although a patient weight over 25 kg is suggested by manufacturers for use of the

<table>
<thead>
<tr>
<th>Table 12.1</th>
<th>Commonly used transesophageal probes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transesophageal probes (selected commercially available devices)</td>
<td>Tip dimensions (W x H x L, in mm)</td>
</tr>
<tr>
<td>Philips</td>
<td></td>
</tr>
<tr>
<td>Pediatric micro-multiplane (S8-3t)</td>
<td>7.5 x 5.5 x 18.5</td>
</tr>
<tr>
<td>Pediatric biplane (no longer supported)</td>
<td>9.3 x 8.8 x 27</td>
</tr>
<tr>
<td>Pediatric mini-multiplane (S7-3t)</td>
<td>10.7 x 8.0 x 27</td>
</tr>
<tr>
<td>Adult 2D multiplane Omni III (S7-2)</td>
<td>14.9 x 12.5 x 35</td>
</tr>
<tr>
<td>Adult 2D/Live 3D xMatrix (X7-2t)</td>
<td>17 x 13.5 x 38</td>
</tr>
<tr>
<td>Siemens</td>
<td></td>
</tr>
<tr>
<td>Pediatric biplane (V7B)</td>
<td>9.5 x 8.5 x 31</td>
</tr>
<tr>
<td>Pediatric multiplane (V7M)</td>
<td>10.7 x 8 x 36*</td>
</tr>
<tr>
<td>Adult multiplane (V5M)</td>
<td>14.5 x 11.5 x 45</td>
</tr>
<tr>
<td>General Electric</td>
<td></td>
</tr>
<tr>
<td>Pediatric multiplane (9T)</td>
<td>10.9 x 8.4 x 35.2</td>
</tr>
<tr>
<td>Pediatric multiplane (9Tc-RS)</td>
<td>10.7 x 7.5 x 37.5</td>
</tr>
<tr>
<td>Adult multiplane (6T)</td>
<td>14 x 12.5 x 45</td>
</tr>
<tr>
<td>Adult multiplane (6Tc)</td>
<td>14 x 12.5 x 45</td>
</tr>
<tr>
<td>Adult multiplane (6Tc-RS)</td>
<td>14 x 12.5 x 45</td>
</tr>
<tr>
<td>Adult 3D/4D (6VT-D)</td>
<td>14.3 x 12.7 x 44.8</td>
</tr>
</tbody>
</table>

H, height; L, length; W, width. Probe specification information provided by respective companies.

Note: The terms “3D” (three-dimensional) and “4D” (four-dimensional) are both used when referring to 3D echocardiography. The term 4D is meant to describe 3D rendering displayed using real-time motion – thus the fourth dimension represents the addition of time. The two terms are used synonymously and interchangeably.
Figure 12.1 The graphic displays the evolution of the transesophageal echocardiography imaging technology from monoplane, to biplane, to multiplane, to three-dimensional (3D) devices. (Source: Texas Children’s Hospital. Reproduced with permission.)

Figure 12.2 The photograph displays four currently available transesophageal echocardiography devices for multiplane imaging in patients with congenital heart disease. (A) Micro-multiplane pediatric probe; (B) mini-multiplane pediatric probe; (C) two-dimensional “adult” or standard probe; (D) three-dimensional “adult” probe.

Table 12.2 Multiplane transesophageal echocardiography (TEE) probe selection based on patient weight

<table>
<thead>
<tr>
<th>TEE probe</th>
<th>Recommended minimal patient weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult TEE (3D)</td>
<td>30</td>
</tr>
<tr>
<td>Adult multiplane (2D)</td>
<td>25</td>
</tr>
<tr>
<td>Pediatric mini-multiplane</td>
<td>3.5</td>
</tr>
<tr>
<td>Pediatric micro-multiplane</td>
<td>2.5</td>
</tr>
</tbody>
</table>

2D, two-dimensional; 3D, three dimensional.

adult 2D TEE probe, this device is frequently used in clinical practice in children weighing less than this. In general, these probes have more piezoelectric crystals than equivalent pediatric devices, and their larger size may allow for improved contact with the esophagus, thus enhancing the overall image resolution. Current 3D TEE imaging probes have slightly larger dimensions than available adult 2D TEE probes, rendering them unsuitable for use in most young children. TEE imaging in neonates, infants, and small children weighing over 3 kg has been safely performed for many years using pediatric multiplane probes (mini-multiplane). A major advance in recent years is the availability of an even smaller device, a pediatric micro-multiplane probe, for use in tiny babies weighing down to 2.5 kg [35]. At the time of writing, the micro-TEE probe, exclusively marketed by Philips Healthcare (Andover, MD, USA), has full 2D and Doppler capabilities [36]. In clinical practice, both of these transducers (mini- and micro-multiplane TEE probes) are also used in even smaller patients than is recommended by the equipment manufacturers [37,38].

Biplane imaging and even monoplane TEE imaging are still performed in infants and children at several centers worldwide, often in countries with limited technologic resources. Intracardiac echocardiography (ICE) catheters (8–10 F) have also been used via the transesophageal approach to image neonates and small infants [39–41]. These catheters are limited to 2D imaging only in a single, longitudinal plane. Although they are not formally marketed for this specific application, reports indicate that they provide clinically useful information in some cases.

At the present time, intraoperative epicardial imaging is reserved for patients in whom TEE probes cannot be used, because of contraindications to esophageal instrumentation, size constraints, or the potential for hemodynamic or respiratory compromise, or in situations where TEE hardware is not available. Drawbacks of the epicardial approach relate to limited windows of interrogation, potential for hemodynamic alterations and rhythm...
abnormalities, risk of infection, and need for expertise in cardiovascular imaging by the surgeon.

**Probe insertion**

In the operating room, the TEE probe is inserted after induction of general anesthesia, endotracheal intubation, and arterial catheter placement. Although aspiration of gastric contents may be standard anesthetic practice in many centers, it has not been found to reliably enhance image quality [42]. In pediatric patients, nasal rather than oral endotracheal intubation may be preferred to better stabilize the endotracheal tube (ETT), with less likelihood of inadvertent extubation or movement during TEE probe manipulation. This practice, however, is variable. Regardless of the intubation route, the ETT should be taped securely to minimize potential displacement.

With the patient’s head in the midline position, the lubricated probe is blindly positioned in the oropharynx and gently advanced into the esophagus. The probe control for transducer tip flexion should be unlocked at this time to allow for free movement. Slight anterior flexion of the probe tip, forward thrusting of the mandible, and device guidance with a gloved finger may aid advancement of the probe along the contour of the posterior pharynx, thereby minimizing trauma. Alternatively, laryngoscopy with direct visualization may be used initially while inserting the probe or if difficult blind-probe insertion is encountered [43].

In children, positioning the head to the side may facilitate the probe’s passage, as this position reportedly results in closure of the ipsilateral pyriform sinus, a site where the probe may encounter obstruction [44]. Once the transducer is placed behind the heart, the patient’s head is repositioned to avoid interference with the surgical field during probe manipulation. Independent factors that render probe insertion difficult in infants weighing 4 kg or less include lower weight, abnormal craniofacial anatomy, prematurity, and a diagnosis of 22q11 deletion [45].

It should be emphasized that probe placement is an essential skill in the practice of TEE. Distinguishing expected from excessive resistance requires thorough expertise and ongoing experience with the technique. Although some degree of effort may be required during esophageal intubation, the probe should never be forced against resistance.

Insertion and manipulation of the probe can be significantly stimulating, so an adequate level of patient sedation/anesthesia/muscle paralysis must be ensured prior to placement. These maneuvers can also be associated with hemodynamic and/or respiratory compromise, particularly in patients with specific anomalies with known significant potential risks of TEE (e.g., anomalous pulmonary venous drainage, vascular rings/slings); thus, vigilance is imperative [46]. In the event of acute hemodynamic or airway changes, the probe should be repositioned or removed immediately.

Outpatient TEE is performed often in adults but rarely in children, as adequate information is obtained from the excellent image quality of TTE, as previously mentioned. In most cases, a specific question needs to be addressed. A combination of oropharyngeal topical anesthesia and intravenous sedation may be sufficient in the adolescent or adult. In younger patients, some adolescents, or, rarely, adults, deep sedation or general anesthesia with endotracheal intubation may be necessary to overcome lack of cooperation, avoid respiratory compromise, and provide adequate time for a complete study.

The facility where TEE is to be performed should be equipped with oxygen, suction capabilities, drugs, and equipment for emergency therapy/cardiopulmonary resuscitation. Standard cardiorespiratory monitoring during the procedure includes intermittent blood pressure measurements, electrocardiography, pulse oximetry, and capnography. Patients with CHD may have significant hemodynamic alterations and be marginally compensated, requiring the judicious, titrated administration of pharmacologic agents [47]. Those with cyanotic heart disease are at additional risk for paradoxical air embolism during the administration of intravenous fluids or drugs. Decreases in systemic vascular resistance associated with a sedative or anesthetic agent can worsen right-to-left shunting and exacerbate underlying systemic arterial desaturation.

**Instrument manipulation**

A TEE probe can be manipulated in several directions to image cardiovascular structures relative to the sagittal plane (Figure 12.3). The probe shaft can be pushed in (advanced) or pulled back (withdrawn) and can be turned to the right (clockwise) or to the left (counterclockwise). Wheel controls on the probe handle are used to manipulate the probe tip, which can be flexed anteriorly (anteflexed) or posteriorly (retroflexed) and to the right or left (Figure 12.4). Pediatric TEE probes may lack the right-to-left control, which is seldom a limitation due to the adequacy of only minimal adjustments in the probe’s position to navigate from view to view. The imaging plane of a stationary, multiplane probe tip can be rotated between angles of 0° and 180°, without the maneuvers required by mono/biplane devices to obtain equivalent views (Figure 12.4) [48].

**KEY POINTS: TEE HARDWARE**

- The TEE technology has evolved from initial mono-plane, to biplane, to multiplane, to recent 3D imaging devices.
- Currently there are four available multiplane probes for TEE imaging in patients with CHD.
- All multiplane probes include 2D, M-mode, spectral Doppler, and color Doppler capabilities.
- Device selection is guided by two main factors: the size of the probe and the weight of the patient being examined.
Several approaches are used for performing a comprehensive TEE examination in the patient with CHD. Each approach presents specific advantages but some potential disadvantages, as described briefly in the sections that follow.

**View-based approach**

The “view-based” TEE examination relies on obtaining several specific pre-defined cross-sections by moving the probe to various locations within the esophagus/stomach. Initial guidelines established by the ASE and Society of Cardiovascular Anesthesiologists (SCA) required a set of 20 TEE views for a comprehensive examination. This approach was widely adopted, becoming standard clinical practice for the TEE examination of the adult patient with an anatomically normal heart [50]. Recently, updated recommendations incorporate eight additional cross-sections, for a total of 28 TEE views (Figure 12.5) [7]. Most, if not all, of these views should be obtained, regardless of sequence, to acquire anatomic, functional, and hemodynamic information during a complete TEE examination. This approach assists in learning the basic principles of TEE and represents an excellent foundation on the subject. The reader is referred to the web-based educational resources of the Toronto General Hospital (www.pie.med.utoronto.ca/TEE/) for interactive modules on the standard TEE examination.

The view-based TEE examination has major benefits, not only as a standardized method of performing the evaluation but also in terms of facilitating teaching, archiving, and reporting of the study, as well as quality assurance. Familiarity with these views, including the nomenclature, where and how they are obtained, the structures displayed by each, and the information derived, enhances one’s ability to perform a detailed examination and to communicate the findings to others. However, several limitations of this approach are recognized. Two
were highlighted in the most recent guidelines, namely: the suggested original TEE views were aimed at the intraoperative interrogation and excluded views that may be necessary in non-operative settings; and the outlined TEE examination was not diagnosis-based, potentially excluding important views in the evaluation of specific common cardiac conditions. These limitations are particularly relevant to the assessment of CHD, as a view-based approach is inadequate for the detailed evaluation of the structural abnormalities in many patients. Standard TEE views may not allow for imaging of the complex anatomic relationships present in congenital pathology. Of critical relevance is the fact that the comprehensive evaluation of many structural anomalies requires not only single views but also sweeps between multiple planes, some non-standard, aimed at building a 3D construct of the anatomic abnormalities.

**Structure-based approach**

The “structure-based” examination focuses on detailed TEE imaging of cardiovascular structures of interest using complementary views to permit their in-depth examination. Specific structural imaging in the adult has been described, for example, in the detailed evaluation of cardiac valves, the Ao, and LAA, among other regions [7,51–57]. A similar type of approach has been extremely helpful in the characterization of specific anatomic and functional abnormalities in the patient with CHD, such as defects that involve the atrial or ventricular septum, pulmonary veins, and other structures [58–60].

This type of image-acquisition paradigm may be preferable in a setting where, for various reasons, a focused TEE examination needs to be performed to address only a specific pathology of concern. One potential limitation of this approach in CHD is that by targeting only particular cardiac structures/pathologies, one may overlook coexisting abnormalities or anatomic variants of relevance.

**Sequential-segmental approach**

The “sequential-segmental” analysis has been proposed as the foundation of complete anatomic assessment in CHD [61–64]. This approach involves a well-organized, methodical interrogation of the three major cardiac segments (atria, ventricles, and great arteries) and their relationships to each other (connections or alignments between the segments), in order to define a patient’s anatomy and any abnormalities (Figure 12.6; also refer to
Figure 12.6 Sequential-segmental approach to congenital heart disease (CHD). The graphic illustrates the steps involved in the sequential-segmental diagnostic analysis to CHD. The approach examines the cardiac situs, position of heart in the thorax, base to apex orientation, segments, and connections. IVC, inferior vena cava; IVS, interventricular septum; L, left; LA, left atrium; LAA, left atrial appendage; LV, left ventricle; MV, mitral valve; PA, pulmonary artery; R, right; RA, right atrium; RAA, right atrial appendage; RV, right ventricle; SVC, superior vena cava; TV, tricuspid valve. Figure courtesy of Ms. Willa Bradshaw.
Chapter 4). This type of analysis has been incorporated into many diagnostic imaging modalities in CHD and is key in echocardiographic assessment (TTE and fetal imaging) [65–68].

The fundamental principle of this methodology is that specific cardiac chambers have characteristic morphologic properties that determine their identities, rather than their positions within the body. The suggested practice examines the arrangement of the thoraco-abdominal organs or situs, atrial structures, ventricles, and great arteries, as well as the connections between the segments, namely, the atrioventricular (AV) and ventriculoarterial (VA) connections [69–71]. This approach has significant merits as congenital heart lesions can have normal or abnormal relationships of chambers, valves, and vessels.

One vital aspect of imaging in CHD is being able to distinguish the morphologic right ventricle (RV) and left ventricle (LV), either of which may function as the systemic or pulmonary ventricle. Characteristic features (Table 12.3) are helpful in distinguishing between the two and not ventricular size, shape, or wall thickness.

The sequential-segmental analysis overcomes limitations of a purely structure-based approach, as all cardiovascular structures are carefully identified and interrogated for a thorough TEE assessment. Despite these advantages, the methodology involved may be less intuitive to those unfamiliar with segmental anatomy and potentially more time-consuming.

**Performance of the examination**

Guidelines exist for the applications of TTE and TEE imaging in CHD [1–3,5,7,49]. However, no uniform consensus or recommendation has been put forward for a standard approach to the TEE examination in the patient with CHD. The updated ASE/SCA TEE guidelines briefly address imaging views in CHD, but only in selected adult patients [7]. In this regard, a recent effort has been undertaken to describe the comprehensive and systematic examination in the patient with CHD, using as a foundation the established ASE/SCA standard views and expanding significantly upon them with additional/modified views [72]. Providing details of the TEE examination in CHD is beyond the scope of this chapter, and therefore only selected aspects will be reviewed and the reader is referred to other publications for an exhaustive discussion on the subject [72–74].

Although a predetermined sequence for the TEE examination in CHD cannot be emphasized and should not be inferred from the outline that follows, it is extremely helpful for individuals to develop their own organized approach in order to perform a complete interrogation in an expeditious manner. The examination may be shortened by unique patient conditions or specific circumstances.

The sections that follow on imaging windows and planes provide a brief overview of selected TEE views frequently obtained during CHD evaluation. The examination assumes levocardia (heart in the left thoracic cavity with apex pointing to the left) and normal segmental anatomy. In other words, viscerotraital situs solitus (stomach on the left, liver on the right, and normal atrial arrangement), concordant AV and VA connections, normal ventricular topology, and great artery spatial orientation are present. To simplify the discussion and to reflect the progression of the technology, the TEE cross-sections are grouped according to their respective imaging planes (transverse, longitudinal, multipane). Not all views can be obtained in all patients, nor will the planes and angles of interrogation necessarily conform to each patient’s unique anatomy. The variety of structural cardiovascular malformations dictates a modified scheme in many cases.

The comprehensive TEE examination in CHD includes detailed 2D imaging and meticulous spectral and color-flow Doppler interrogation. Contrast echocardiography using an injection of agitated saline or 5% albumin into a peripheral or central vein can detect small intracardiac shunts, further delineate anatomy (e.g., persistent left superior vena cava [SVC] to coronary sinus connection), and identify pathology such as atrial baffle leaks [75].

**Imaging windows**

During a TEE examination in CHD, the heart and related vascular structures are imaged at multiple levels (Figure 12.7): upper esophageal (UE), mid-esophageal (ME), lower esophageal (LE), transgastric (TG), and deep transgastric (DTG), using different transducer angles to obtain specific cross-sections. These diverse TEE windows complement each other and allow for information that is not otherwise obtainable in some views. Examination from the LE window (an additional probe position from the four described in the guidelines document) allows for segmental anatomic evaluation in CHD. The TG and DTG views, for example, provide favorable alignment of the Doppler angle of interrogation to the outflow tracts, optimizing spectral Doppler signals and the assessment of gradients.

**Planes of interrogation and corresponding views**

Suitable imaging planes for TEE evaluation of the patient with CHD include those that allow for the ASE/SCA standard views (Figure 12.5) in addition to planes that display complementary cross-sections (Figure 12.8). Although the examination assumes the use of a multiplane device, it should be reiterated that any image at a transducer angle of 0° can be obtained using a monoplane or biplane probe, and at 90° using a biplane probe [76,77].

<table>
<thead>
<tr>
<th>Table 12.3 Characteristic anatomic features of the right and left ventricles</th>
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<tbody>
<tr>
<td><strong>Right ventricle</strong></td>
</tr>
<tr>
<td>Atrioventricular valve</td>
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<tr>
<td>Annulus location</td>
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<tr>
<td>Wall trabeculations</td>
</tr>
<tr>
<td>Moderator band</td>
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<tr>
<td>Infundibulum</td>
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</tbody>
</table>
Transverse plane imaging

The transverse plane images the heart at 0° by advancing and withdrawing the TEE probe to various levels within the esophagus and stomach. Once the probe is positioned in the mid-esophagus, the ME four-chamber (ME 4 Ch) or ME five-chamber (ME 5 Ch) view is displayed (Figure 12.5, ME LV and MV [mitral valve] views). These views often are obtained by manipulating the probe (tip or shaft adjustments) or adjusting the transducer angle on a multiplane probe. The ME 4 Ch view interrogates all four cardiac chambers, AV valves, and atrial and ventricular septae. The ME 5 Ch view, obtained by probe tip anteflexion or slight withdrawal of the probe from the ME 4 Ch view, also displays the left ventricular outflow tract (LVOT) and proximal Ao.

Further withdrawal and anteflexion of the probe from the ME 5 Ch view displays the ME ascending aortic short-axis view (ME asc Ao SAX), where the proximal ascending Ao is seen in its short axis and the main pulmonary artery (MPA) in its long axis (Figure 12.5, thoracic aorta views). It reflects the usual “criss-cross” relationship of the great arteries in the normal heart. The ME asc Ao SAX view also provides excellent anatomical visualization of the right pulmonary artery (RPA) and allows for corresponding Doppler assessment. The SVC in this view is seen in its short axis to the right of the mid-ascending Ao. The MPA bifurcation and proximal branch pulmonary arteries (PAs) can be interrogated in most patients by advancing the probe either in an upper esophageal position (Figure 12.8A,B) or after the ME 4 Ch view has been obtained, by further withdrawal of the probe into the upper esophagus to obtain the UE pulmonary artery long-axis view (UE PA LAX). Although not part of the formal guidelines, this view is of particular interest in CHD, given the high frequency of abnormalities affecting the main and/or branched PAs. Turning the probe shaft to the right and left from this window enhances visualization of the right and left branches, respectively. Interposition of the left mainstem bronchus, however, renders imaging of the left pulmonary artery (LPA) somewhat difficult.

In the ME 4 Ch view, rightward (clockwise) turning of the probe displays the right-sided pulmonary veins, SVC, and mid-ascending Ao in the ME right pulmonary vein view (ME Rt Pulm Vein) (Figure 12.5, ME views), whereas, leftward (counterclockwise) turning of the probe displays the left-sided pulmonary veins and LAA; further turning posteriorly reveals the descending Ao in short-axis (desc Ao SAX) view (Figure 12.5, thoracic aorta views). Withdrawing the probe into the upper esophagus images the aortic arch in long-axis (UE Ao Arch LAX) (Figure 12.5, thoracic aorta views, and Figure 12.8A).

Advancing the probe from the mid (ME 4 Ch) to the distal esophagus displays the LE situs short-axis view (LE Situs SAX) (Figure 12.8E), showing the inferior vena cava (IVC) in short axis, and, by withdrawal of the probe, confirming its entry into the right atrium (RA) in the structurally normal heart. This view also displays the coronary sinus as it courses posteriorly in a nearly horizontal plane. As previously noted, this view facilitates the evaluation veno-atrial connections in CHD.

Advancement of the TEE probe into the stomach combined with maximal anteflexion allows for transgastric imaging with multiple cross-sectional short-axis views of the LV at different levels using the transverse plane (Figure 12.5, transgastric [TG] views): basal (TG basal SAX), mid-papillary (TG mid SAX), and apical (TG apical SAX). These views, in particular the TG mid SAX, are extremely helpful in the evaluation of LV function (global and segmental) and adequacy of volume. Adjusting the probe tip in the TG window (flexion controls) and rotating the probe shaft allows for oblique sections of the RV to be obtained, as well as images of the right ventricular outflow tract (RVOT) and proximal MPA trunk as it courses anteriorly across the heart surface. These are referred to as the TG right ventricular basal (TG RV Basal) and TG right ventricular inflow-outflow views (TG RV In-Out) (Figure 12.5, transgastric views)

Further advancement of the probe into the fundus of the stomach with variable degrees of tip anteflexion obtains the DTG five-chamber view (DTG 5 Ch; Figure 12.5, transgastric views), referred to in the prior guidelines as the DTG long-axis view. This cross-section displays the LV from base to apex, being equivalent to the ME 5 Ch view. In most pediatric centers, the DTG views are up-down inverted (DTG 5 Ch modified; Figure 12.8G) in order to display the TEE images in an anatomic orientation.
In addition to the 28 views suggested in the American Society of Echocardiography/Society of Cardiovascular Anesthesiologists (ASE/SCA) guidelines for a comprehensive transesophageal echocardiographic examination (refer to Figure 12.5), several other views, as shown, are to be considered in the assessment of the patient with congenital heart disease (refer to the text for further discussion). (Source: Texas Children’s Hospital. Reproduced with permission.) (Source for panels A and C (marked by asterisks): Hahn et al. [4]. Reproduced with permission of Elsevier.)
Longitudinal plane imaging

The longitudinal plane displays long-axis views of the heart using biplane or multiplane (at 90° transducer angle) TEE imaging [77,78]. The ME two-chamber view (ME 2 Ch) depicting the left atrium (LA) and LV can be obtained by rotating the imaging plane perpendicular to the ME 4 Ch view (Figure 12.5, mid-esophageal LV and MV views). From the ME 2 Ch view, turning the probe to the right while still in the longitudinal plane initially displays portions of the LVOT and the ascending Ao. Further turning of the probe reveals the ME bicaval view (ME Bic) (Figure 12.5, mid-esophageal views) with the interatrial septum (IAS) and entrance of the SVC and IVC into the RA. The pulmonary veins can be examined in this plane at the UE level by turning the probe shaft clockwise or counterclockwise to obtain the UE right and left pulmonary vein views (UE Rt and Lt Pulm Veins) for the right and left pulmonary veins, respectively (Figure 12.5, mid-esophageal views). Advancing the probe to the mid-esophagus while examining the left-sided pulmonary veins allows for the LAA to be visualized in the ME left atrial appendage view (ME LAA view) (Figure 12.5, mid-esophageal views).

Further advancing the probe from this level into the lower esophageal window allows for the LE inferior vena cava long-axis view to be obtained (LE IVC LAX) (Figure 12.8F) and examination of the lower aspect of the IAS, RA, and entry of the hepatic veins into the IVC. Views of both ventricles in the 90° plane can be demonstrated by further advancing the TEE probe into the stomach (TG and DTG levels) (Figures 12.5, transgastric views, and Figure 12.8H).

The longitudinal imaging plane can also facilitate the evaluation of the Ao at multiple levels (Figure 12.5, thoracic aorta views): in the upper esophagus, to display the aortic arch short-axis view (UE Ao Arch SAX) where the aortic arch, PA, and innominate vein are seen; in the upper to mid-esophagus, to demonstrate the ascending Ao in long-axis (ME asc Ao LAX); and in the ME/TG levels by rotating the TEE probe posteriorly, to assess the descending Ao in long-axis (desc Ao LAX). The distal LPA can be interrogated in a modified view by further advancing the probe and turning it to the left once the UE Ao Arch SAX view is obtained (Figure 12.8C).

Multiplane imaging

Cardiac structures that are inadequately visualized using the imaging planes outlined above can be displayed by adjusting the transducer angle to better align the interrogating plane. The control to change the multiplane angle in adult devices is electronic, whereas it can be either mechanical (manual) or electronic in pediatric devices (Figure 12.9). As noted, a significant advantage of multiplane imaging in CHD is that it assesses structures that do not follow the usual interrogation planes of the normal heart and obtains additional views not feasible with monoplane/biplane probes. The multiplane approach is also particularly useful to examine the cardiac valves from the ME window.

The aortic valve (AoV) is seen in short axis at ~30° in the ME AoV short-axis view (ME AoV SAX) and in long axis at ~120° in the ME AoV long-axis view (ME AoV LAX) (Figure 12.5, mid-esophageal views). The tricuspid valve (TV), in addition to being seen in the ME 4 Ch view at 0° as noted earlier, can also be interrogated in the ME right ventricular inflow-outflow view (ME RV In-Out) at ~60° and ME modified bicaval TV view (ME Mod Bic TV) at 50°−70° (Figure 12.5, mid-esophageal views). The MV is seen in
multiple ME views: ME 4 Ch (0°), ME mitral commissural (60°, ME MV Comm), ME 2 Ch (90°), and ME long-axis (120°, ME LAX) (Figure 12.5, mid-esophageal LV and MV views). The pulmonary valve (PV) is viewed in the ME RV In-Out (60°), and UE Ao Arch SAX (70°–90°). The valves can also be interrogated in complementary cross-sections obtained from the TG windows as follows: for MV the TG two-chamber view (TG 2 Ch at ~ 90°–110°); for the AoV the TG long-axis view (TG LAX at ~120°–140°); and for the TV the TG RV inflow view (TG RV In) (Figure 12.5, transgastric views).

Three-dimensional TEE

Ease of acquisition with rapid online display of detailed dynamic images has allowed real-time 3D TEE to be used increasingly in the perioperative period to assess cardiac anatomy and function [79]. Special matrix array ultrasound probes acquire raw data by volume scanning, and integrated ultrasound software processes the 3D datasets. These TEE probes perform all standard 2D functions, include motion mode (M-mode) and all Doppler modalities (spectral, color, tissue), and have an additional feature of multiplane mode (X-Plane) to simultaneously display independent 2D scanning planes during the same heartbeat. Single-button activation of specific 3D imaging modes for both TEE and TTE matrix array probes include: live, zoom, full volume, and color Doppler full volume (Table 12.4). Using these modes, a specific region of interest (ROI) can be defined and a 3D volume of varying sizes obtained. Newer software can display all 3D datasets in real time, such that movement of the probe will immediately affect the 3D volume on the display.

Currently, all real-time 3D imaging modes appear as a volume-rendered 3D object with full details of the surface and inner structure. Any rendered 3D object can be freely rotated in the display and shown from any orientation, including the surgeon’s perspective. Cropping permits a “virtual dissection” of the 3D object that examines all its details.

The 3D technology has proven superior to 2D echocardiography for assessment of the LV (volume, ejection fraction, mass, and dyssynchrony) and the MV [80]. En face views of the MV, for example, when displayed in the surgeon’s orientation viewed from the LA, allow anatomic details of the leaflets and better define the pathology involving prolapse, clefts, and perforations [81,82]. Thus, the use of this modality has become well accepted for adult patients undergoing cardiothoracic surgical interventions and catheter-based procedures. The excellent detail of 3D imaging provides additional information about cardiac anatomy and spatial relationships compared with 2D echocardiography, clearly a merit of the technology in the evaluation of CHD. Real-time 3D TEE can better demonstrate the intricate relations of cardiac structures in patients with complex CHD. Whereas multiple 2D views were needed previously to assess pathology, the entire heart can be seen by 3D imaging in a single screen display. Real-time 3D TEE has been demonstrated to better define the shape and spatial relations of a PFO or ASD with surrounding structures such as the AoV and great vessels [58,59]. The use of 3D TEE to guide placement of percutaneous device closure of intracardiac communications, including not only ASD, but also VSD, and paravalvular leaks of prosthetic valves has been well described [15,83].

Despite the limited experience of real-time 3D TEE in children with CHD due to the lack of suitable imaging

### Table 12.4 Real-time three-dimensional transesophageal echocardiography imaging

<table>
<thead>
<tr>
<th>Structure</th>
<th>2D view for 3D acquisition</th>
<th>3D mode</th>
<th>Clinical utility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitral valve</td>
<td>ME 4 Ch (0°), ME MV Comm (60°), ME 2 Ch (90°), ME LAX (120°) ± CD</td>
<td>Zoom, FV</td>
<td>Morphology, function, quantification (effective regurgitant orifice area, MV area)</td>
</tr>
<tr>
<td>Aortic valve</td>
<td>ME AoV SAX (30°–60°), ME AoV LAX (120°) ± CD</td>
<td>Zoom</td>
<td>AoV area, TAVI</td>
</tr>
<tr>
<td>Tricuspid valve</td>
<td>ME 4 Ch (0°–30°), TG (40°) ± CD</td>
<td>Zoom</td>
<td>Unstudied</td>
</tr>
<tr>
<td>Pulmonary valve</td>
<td>UE Ao Arch SAX (90°) ± CD</td>
<td>Zoom</td>
<td>TEE has limited views</td>
</tr>
<tr>
<td>Interatrial septum</td>
<td>ME 4 Ch (0°), ME Bic (90°)</td>
<td>Zoom, FV</td>
<td>ASD</td>
</tr>
<tr>
<td>Left ventricle</td>
<td>ME 4 Ch (0°), ME 2 Ch (90°), ME LAX (120°)</td>
<td>FV</td>
<td>Volume, mass, ejection fraction, dyssynchrony</td>
</tr>
<tr>
<td>Right ventricle</td>
<td>ME 4 Ch (0°), ME 2 Ch (90°), ME LAX (120°)</td>
<td>FV</td>
<td>Volume, ejection fraction</td>
</tr>
<tr>
<td>Left atrial appendage</td>
<td>ME 4 Ch (0°), ME 45°, MV Comm (60°), ME 2 Ch (90°), ME LAA (110°)</td>
<td>Live, Zoom</td>
<td>Thrombus</td>
</tr>
</tbody>
</table>

AoV, aortic valve; ASD, atrial septal defect; Bic, bicaval; CD, color Doppler; Comm, commissural; FV, full volume; LAA, left atrial appendage; LAX, long-axis; ME, mid-esophageal; MV, mitral valve; SAX, short-axis; TAVI, transcatheter AoV implantation; TG, transgastric; UE Ao Arch, upper esophageal aortic arch; 2 Ch, two-chamber; 4 Ch, four-chamber; 2D, two-dimensional; 3D, three-dimensional.

The baseline 2D TEE view is used with different 3D imaging modes to scan a region of interest and obtain a volume of tissue. This volume or block of tissue can be cropped, rotated and displayed in any orientation to show normal and pathologic findings.
devices, extremely favorable data have been generated thus far on the applications of the technology in the patient with a congenitally malformed heart [59,84–88], mirroring the reported 3D TTE experience in CHD [89]. Although outlining specific indications for 3D TEE imaging in CHD is not possible at this time, a reasonable proposal is that this modality should be considered in cases for which a 3D perspective may offer additional benefits over routine 2D TEE in the patient able to be interrogated with currently available devices.

Similar to 2D TEE, structures closest to the probe are easily imaged in 3D, enabling the evaluation of clinically relevant issues in real time (Table 12.4). The thin IAS and distant structures (AoV and PV) remain difficult to image by 3D TEE in some patients. Despite recent recommendations for 3D echocardiographic image acquisition and display, there remains a lack of a standardized protocol for the use of intraoperative real-time 3D TEE in everyday practice [79]. Although 3D image acquisition is rapid, analyzing the 3D datasets, in particular, with analytical software can be time-consuming and challenging in the hectic intraoperative environment.

**Functional assessment**

Assessments of ventricular systolic and diastolic function are important components of a comprehensive TEE examination. The ventricles differ in geometry, systolic contraction pattern, and load conditions, requiring each to be assessed using different methods. Quantitative assessment of LV systolic function using echocardiography relies on geometric models that may not be applicable to the unusual ventricular geometries present in CHD [90,91]. In patients with CHD, increases in the size of the RV size and deterioration of function often determine the need for clinical intervention [92]. The current gold standard for accurate determination of ventricular systolic function, in particular the RV, is cardiac MRI, although real-time 3D echocardiography has improved accuracy for assessing LV function [79].

Newer echocardiographic techniques can quantify subtle changes in regional and global ventricular function, independent of ventricular morphology and less dependent on loading conditions [93]. **Tissue Doppler imaging** (TDI), also referred to as Doppler tissue imaging (DTI), provides a non-geometric quantitative measure of both systolic and diastolic ventricular functions that are easily obtained, reproducible, and clinically valid [94]. **Strain and strain rate imaging** can provide global and regional assessment of ventricular function that is independent of geometry and less dependent on loading conditions [95–97]. Improved ultrasound technology has simplified techniques such as tissue Doppler, 3D ejection fraction, and tissue tracking for strain/strain rate to allow more discriminating quantification of systolic function in the operative setting. For many of these techniques, reference values have been established in normal adults and children, most often using TTE [90,91,98].

### Left ventricular systolic function

Normal LV function involves complex 3D movements during the cardiac cycle. Systolic function depends on heart rate, myocardial contractility, and loading conditions. Typically, LV function is assessed quantitatively using echocardiography by measuring changes in LV volume with calculation of stroke volume (SV), ejection fraction (EF), and cardiac output (CO). However, these quantitative measures are time-consuming, limited by loading conditions, and affected by alterations in geometric shape. Technical concerns when using TEE, such as chamber foreshortening and poor endocardial definition, further challenge the acquisition of quantitative information. Thus qualitative assessment by “eyeballing” and methods such as simple linear (shortening fraction) and area (fractional area change) measurements are often used in the operating room to determine ventricular systolic performance.

The TG SAX and LAX views are used to qualitatively assess ventricular systolic function by “eyeballing” wall motion and thickening. Although used ubiquitously, this subjective technique lacks standardization, depends on experience, and has significant inter- and intra-observer variability. The TG mid SAX view is frequently used but examines only a portion of the LV (six segments) and may not reflect global systolic function in the presence of abnormal geometric shape or regional wall motion abnormalities.

**Shortening fraction** (SF) estimates LV systolic function from linear measures of end-diastolic (LV EDD) and end-systolic (LV ESD) internal cavity dimensions using M-mode in a TG mid SAX view of the LV (Figure 12.10A). The superior temporal resolution of M-mode echocardiography allows for representation of movement of structures over the course of time. The SF as a percentage (normal: 26–45%) is determined by the formula:

$$SF(\%) = \frac{(LV\ EDD - LV\ ESD) \times 100}{LV\ EDD}$$

**Fractional area change** (FAC) estimates global LV systolic function using area measurements; thus, it is not the EF, as it is not a volume measurement. FAC is obtained by tracing the LV endocardial border to obtain an area at end-diastole (LV EDA) and end-systole (LV ESA) from LAX (ME view) or SAX (TG view) LV cross-sections (Figure 12.10B). The LV FAC expressed as a percentage (normal: 45%) is determined by the formula:

$$LV\ FAC\ % = \frac{(LV\ EDA - LV\ ESA) \times 100}{LV\ EDA}$$

**Ejection fraction** represents the most commonly measured index of ventricular systolic function by echocardiography.
The LV EF as a percentage (normal range: 56–78%) can be calculated as follows:

\[
\text{LV EF \%} = \frac{(\text{LV EDV} - \text{LV ESV}) \times 100}{\text{LV EDV}}
\]

The end-diastolic volume (EDV) and end-systolic volume (ESV) of the LV can be determined using 2D geometric methods and, more recently, from 3D volumes. The Simpson’s method of discs (MOD) is used in the ME 4 Ch and 2 Ch views (single or biplane method) to divide the LV into slices of known thickness, whereby the sum of the slices represents the LV volume. The LV cavity is traced at end-diastole and end-systole, and the LV length through the apex is indicated (Figure 12.10C). The ultrasound machine software automatically determines the LV volumes, SV, and EF.

A full volume dataset acquired using 3D imaging can assess LV volume using two methods: 3D-guided biplanes or direct volumetric analysis. The 3D-guided biplane method minimizes foreshortening of the LV by positioning two perpendicular 2D planes accurately through the LV apex, thereby creating ideal ME 4 Ch and 2 Ch views. LV volume, EF, and mass are calculated by applying the modified Simpson’s biplane MOD. Using specialized software available on the ultrasound system, direct volumetric analysis measures LV volume throughout the cardiac cycle from a 3D surface-rendered cast of the LV cavity (Figure 12.10G). The EDV and ESV are

![Figure 12.10](image-url)
measured, and the SV and EF are calculated. This method more accurately quantifies LV volumes, particularly in patients with an abnormal ventricular shape or regional wall motion abnormalities. This benefit in part relates to better alignment through the cardiac apex, inclusion of more endocardial surface during analysis, and the lack of geometric shape assumption. The accuracy of 3D TTE in measuring LV and RV volumes is comparable to 2D TTE, MRI, and CT techniques. The assessment of ventricular function using the 3D technology as described is of great benefit in CHD and in particular in patients with single ventricle anatomic variants.

*Doppler estimation* of LV SV and CO can be obtained using the spectral Doppler modality. Any intracardiac site where both the cross-sectional area (CSA) and the flow velocity time integral (VTI) can be recorded allows for SV determination as $SV = CSA \times VTI$. This method can be applied easily by measuring the diameter of the AoV annulus (ME AoV LAX view) and flow through the valve (DTG 5 Ch view). As the CSA of the AoV annulus does not usually change, SV (and CO) can be serially monitored by changes in the VTI. Cardiac output is calculated as the product of SV and heart rate.

*Tissue Doppler imaging* records and displays pulsed-wave Doppler signals produced by the low-velocity movement of tissue. Positioning the sample volume at the lateral or septal mitral annulus measures and displays peak myocardial velocity (Figure 12.10D). Obtaining a clean spectral trace depends on parallel Doppler alignment and tissue devoid of artifacts from reverberation, side lobes, or dropout. The TDI spectral display of the mitral annulus comprises a systolic velocity ($S'$) and two opposite-directed velocities, in early diastole ($E'$) and late diastole ($A'$). The $S'$ velocity is an estimate of LV EF but is not specifically a measure of contractility. Normal values for TDI in pediatric and adult patients differ with heart rate, age, ventricular morphology, and loading conditions. The strong age-dependence of TDI velocities in children along with the many factors that complicate the assessment of these parameters in this age group account for the relatively slow incorporation of this modality into pediatric non-invasive functional evaluation [98].

**Regional wall motion**

Dividing the LV into segments more accurately describes regional wall motion abnormalities with correlation to coronary artery anatomy. Analysis of LV segmental function is based on a qualitative visual assessment for motion and/or thickening of a segment during systole. The ASE and SCA use a 17-segment LV model dividing the basal and mid-levels into six segments each and the apex into four, with an apical cap (devoid of LV cavity) as the 17th segment [90,99]. TG SAX views show one LV level at a time, but they have the advantage of simultaneously viewing portions supplied by all major coronary arteries (right, left anterior descending, and circumflex vessels). The use of additional TEE views complements this assessment (Figure 12.11).

As in the case of adults, regional wall motion abnormalities detected by TEE in pediatric patients can be considered a surrogate of compromised myocardial blood flow [100,101]. Segmental abnormalities can occur due to surgical manipulations that alter coronary blood flow either during the dissection or as a result of interventions involving the Ao or coronary arteries, intracoronary air, or localized reperfusion injury during cardiac surgery.

**Strain and strain rate**

Newer echocardiographic modalities, such as strain and strain rate imaging, offer an enhanced approach to the evaluation of regional myocardial contraction and relaxation. During systole, the actual volume of myocardial tissue remains unchanged, but the myocardium changes in shape or deforms in three dimensions: longitudinal (shortening), radial (thickening), and circumferential (shortening and torsion). Strain and strain rate analyze ventricular deformation to more accurately quantify global and regional ventricular function [95,96,102,103]. *Strain* is a single dimensionless (%) parameter that examines the motion deformation between two points in the myocardial wall. Total deformation in all dimensions is related to a percentage change from the initial length. Negative strain implies that the fibers shorten (circumferential plus longitudinal) or thin (radial), whereas positive strain indicates that the fibers lengthen (circumferential plus longitudinal) or thicken (radial). End-systolic strain estimates EF. *Strain rate* is the speed of deformation or the change in strain over time (1/s). Peak systolic strain rate is a measure of contractility.
Two methods can assess myocardial deformation: TDI and speckle tracking. Speckle tracking of myocardium from a standard 2D image quantifies myocardial deformation without the limitations of angle dependence associated with TDI. Speckle tracking involves frame-by-frame analysis of the movement of a region of speckles of the myocardium to derive their direction and velocity (shift over time) of tissue movement relative to each other. Speckle tracking is less influenced by artifacts, although reverberations and dropout of myocardial tissue are problematic. Speckle tracking displays peak strain as an average value for each regional wall. Averaging these peak strain values provides the global longitudinal peak systolic strain (GLPSS), a measure of global systolic function. The distribution of regional peak systolic and global systolic strain is often displayed using a colorized bull's-eye format (Figure 12.10f). The analysis of myocardial deformation has been applied to various cardiovascular diseases, including cardiomyopathy and valve pathology. In recent years, this assessment has been extended to the perioperative setting, utilizing TEE; however, the experience to date has been limited [97].

Right ventricular systolic function
The assessment of RV systolic function by echocardiography is complicated by its non-geometric, asymmetric, crescent shape, which precludes easy application of quantitative methods [104,105]. Despite these challenges, several approaches have been applied to this assessment [106–108]. The most commonly used echocardiographic approaches for functional evaluation are RV FAC and tricuspid annular plane systolic excursion. Tissue Doppler and strain echocardiography have also been used following the same principles described earlier but evaluating the RV instead [109]. Qualitative assessment of RV size and function may be augmented by Doppler measurement of the RV myocardial performance index (RV MPI). As previously mentioned, MRI is the current reference standard for the assessment of RV volume and systolic function. The RV FAC can be obtained using a formula of area measurements similar to that used for the LV FAC, by tracing the endocardial border of the RV during systole and diastole from the ME 4 Ch view. Normal values for RV FAC are 35–60%, for mild dysfunction 25–35%, for moderate dysfunction 18–24%, and for severe dysfunction <17%.

Tricuspid annular plane systolic excursion is the distance of systolic excursion of the lateral TV annulus in a longitudinal plane, often measured using M-mode. It is a surrogate measure of global RV function (normal: 16–30 mm in adults) that correlates with angiography, biplane MOD, and FAC. Unlike TTE, it may be difficult to achieve parallel alignment in the ME 4 Ch view for M-mode assessment; as an alternative, the TG RV In view may offer better alignment.

The MPI, also known as the Tei index, is a Doppler-derived measure of global ventricular function. It incorporates both systolic and diastolic time intervals and thus represents both systolic and diastolic performance [110]. The MPI is defined as the sum of isovolumic contraction time (ICT) and isovolumic relaxation time (IRT) divided by ejection time (ET):

$$\text{MPI} = \frac{\text{ICT} + \text{IRT}}{\text{ET}}$$

The longer the isovolumic times, the higher the MPI and the worse the ventricular performance.

This index is easily measured for either the LV or RV from pulsed-wave Doppler interrogation of the respective AV valve and outflow tract (Figure 12.10E). The index can also be derived using tissue Doppler (TDI-MPI) over a single cardiac cycle, thereby increasing its accuracy compared with the conventional Tei index. Studies have established normal MPI values for both adults and children (normal values in adults: LV, 0.39 ± 0.05 and RV, 0.28 ± 0.04; normal values in children: LV, 0.35 ± 0.03 and RV, 0.32 ± 0.03) [111,112]. This index has been applied to the assessment of LV and RV function in patients with CHD, as well as in the evaluation of complex ventricular geometries [112–114]. It has also been used in the intraoperative setting to compare the cardiovascular effects of anesthetics agents in children with CHD [115].

Evaluation of diastolic function
Diastolic dysfunction plays a major role in cardiovascular disease and is considered a risk factor influencing clinical outcomes [116]. Congenital and acquired pathologies in the pediatric age group, as well as in adults with CHD, represent no exception to the presence of diastolic abnormalities.

The echocardiographic assessment of diastolic function has been described extensively in the literature and detailed in ASE guidelines [117–119]. LV diastolic function can be evaluated using transmitial inflow Doppler indices (E, A, deceleration time) and tissue Doppler mitral annular velocities (E', A') at the lateral mitral annulus [120]. These values, along with other Doppler echocardiographic variables (e.g., pulmonary venous flows), can be combined to classify patterns of diastolic dysfunction and to assess progression of disease. In a similar way, RV diastolic function can be evaluated from tissue Doppler of tricuspid annular velocities.

Unfortunately, the evaluation of diastolic function in pediatric patients has met several challenges due to the many confounding variables that influence appropriate Doppler assessment and interpretation of findings. Although the perioperative evaluation of diastolic function in patients undergoing cardiac surgery has been reported in adults [120,121], concerns remain regarding the application of TTE-derived values in awake patients to a setting where TEE is used under the conditions of...
general anesthesia. No formal studies have explored diastolic function using TEE in children or, specifically, in the CHD population.

Hemodynamic evaluation

Echocardiography is an excellent non-invasive tool to obtain semi-quantitative and quantitative hemodynamic information in CHD [122]. Doppler assesses blood flow and displays it as color superimposed over a 2D image (color Doppler) or as a spectral graph of velocity over time (spectral Doppler). Information obtained from Doppler can derive measures of pressure, volume, and flow [123].

Spectral Doppler measures the velocity of blood at a specific position, using a sample volume of pulsed-wave Doppler or along a sample line with continuous-wave Doppler. Doppler measurements by echocardiography require adequate alignment to the direction of blood flow to minimize underestimation. The spectral Doppler display can be traced to yield values for peak and mean velocities and the area under the curve, the flow VTI. Doppler waveforms should be displayed at a sweep speed of 100–150 mm/s to discriminate temporal changes in the velocity flow profile, particularly in children with fast heart rates.

The complete Bernoulli equation is a complex formula that incorporates Doppler velocity measurements, flow acceleration, and viscous friction (blood viscosity) to estimate the peak instantaneous pressure gradient (PG) across an orifice. In clinical practice, a simplified version of the Bernoulli equation is sufficient in most cases to estimate the PG from the measured peak velocity (V) as follows:

$$\Delta P = 4V^2$$

Good correlation has been documented between Doppler estimates of PGs and direct pressure measurements. Preoperative determination of PGs obtained when patients are awake or lightly sedated may differ from those obtained in the operating room under general anesthesia and conditions that may influence ventricular loading and/or systolic function.

No echocardiographic technique measures intracardiac pressures directly. Instead, it is necessary to use Doppler velocity measurements of regurgitant jets or across structures and apply the modified Bernoulli equation \( \Delta P = P_1 - P_2 = 4(V_2^2 - V_1^2) \) to determine a pressure drop or gradient. In most cases, \( V_2 \) is significantly higher than is \( V_1 \), so the \( V_1 \) component of this equation can usually be neglected. This technique is particularly valuable for estimating right ventricular systolic pressure (RVSP), which should reflect the pulmonary artery systolic pressure (PASP) in the absence of obstruction to RV outflow, and can determine the presence of pulmonary hypertension.

**Table 12.5** Doppler parameters in severe valvular disease

<table>
<thead>
<tr>
<th></th>
<th>Aortic</th>
<th>Mitral</th>
<th>Tricuspid</th>
<th>Pulmonic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Severe regurgitation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CW Doppler signal strength</td>
<td>Dense</td>
<td>Dense</td>
<td>Dense</td>
<td>Dense</td>
</tr>
<tr>
<td>JA mapping (cm²) or JA/LVOT(%)</td>
<td>&gt;60</td>
<td>&gt;10</td>
<td>&gt;10</td>
<td></td>
</tr>
<tr>
<td>LA atrial area or IH/LVOT(%)</td>
<td>&gt;65</td>
<td>&gt;40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doppler flow reversal</td>
<td>desc aorta</td>
<td>S pulmonary vein</td>
<td>S hepatic vein</td>
<td>PA</td>
</tr>
<tr>
<td>Regurgitant volume (mL)</td>
<td>≥60</td>
<td>≥60</td>
<td>≥60</td>
<td>≥60</td>
</tr>
<tr>
<td>Regurgitant fraction (%)</td>
<td>≥50</td>
<td>≥50</td>
<td>≥50</td>
<td>≥50</td>
</tr>
<tr>
<td>Vena contracta width (mm)*</td>
<td>6</td>
<td>≥7</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Effective regurgitant orifice area (cm²)</td>
<td>≥0.30</td>
<td>≥0.4</td>
<td>≥0.4</td>
<td></td>
</tr>
<tr>
<td>PISA radius (mm)**</td>
<td></td>
<td>&gt;10</td>
<td>&gt;9</td>
<td></td>
</tr>
<tr>
<td>PHT (ms)</td>
<td>&lt;200–300</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Severe stenosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Velocity (m/s)</td>
<td>&gt;4</td>
<td>&gt;3</td>
<td>&gt;1.5</td>
<td>&gt;4</td>
</tr>
<tr>
<td>Mean pressure gradient (mmHg)</td>
<td>&gt;40</td>
<td>&gt;10</td>
<td>&gt;5</td>
<td>See note</td>
</tr>
<tr>
<td>Valve area (cm²)</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>PHT (ms)</td>
<td>&gt;220</td>
<td>&gt;195</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Severity of valve regurgitation or stenosis can be assessed using different spectral and color Doppler modalities. Adult values for severe disease of different cardiac valves are shown. **Valvular regurgitation**: Color Doppler can be used to map the area of a regurgitant jet, measure the vena contracta or narrowest region of the regurgitant jet (corresponds to the diameter of the regurgitant orifice area) and the PISA radius (based on the principle of flow convergence zone corresponding to regurgitant flow). Spectral Doppler of the regurgitant jet signal strength by continuous-wave, systolic flow reversal in major vessels, and PHT (time needed for the peak transvalvular pressure gradient to fall to half its value) can be measured to assess severity. The regurgitant volume, fraction, and effective regurgitant orifice area can be calculated. **Valvular stenosis**: Spectral Doppler allows for assessment of velocity and pressure gradient, calculation of valve area, and PHT. CW, continuous-wave; desc, descending; JA, jet area; JH, jet height; LVOT, left ventricular outflow tract; PISA, proximal iso-velocity surface area; PHT, pressure half-time. Note: for pulmonic valve, peak pressure gradient (mmHg) >64

Nyquist limits: *, 50–60cm/s; **, 40 cm/s. Pulmonic valve = pulmonary valve.
The peak velocity of the tricuspid regurgitant ($V_{TR}$) jet is used along with an estimate of right atrial pressure (RAP) in the following equation:

$$RVSP \text{ (in mmHg)} = 4V_{TR}^2 + \text{RAP}$$

Color Doppler facilitates the detection of abnormal flows and can assess severity of disease (Table 12.5). Measurements of the jet area, vena contracta, and the region of flow acceleration are used in combination to grade the severity of regurgitant valvular lesions [124–126].

*Shunt fractions* can be calculated by measuring flow (Q) through the pulmonary (Qp) and systemic (Qs) circulations. Flow is measured typically across the PV and AoV from the Doppler-derived VTI and the CSA of each arterial root as:

$$Q = VTI \times CSA$$

Transesophageal echocardiography is a reliable monitor of LV filling (preload) changes in all age groups. In pediatric patients, experienced echocardiographers can identify with high sensitivity and specificity mild reductions in blood volume by changes in LV EDA using TEE in the TG mid SAX view [127]. A marked decrease in both EDA and ESA suggests hypovolemia. Conditions such as arterial vasodilation, severe aortic regurgitation, mitral regurgitation, and the presence of a VSD may have a reduced ESA but typically have a normal to increased EDA in this TEE view.

### Applications of TEE in CHD

#### Intraoperative setting

The benefits of using TEE during surgery for CHD include monitoring, assessment of the adequacy of cardiac de-airing, detection of complications, and guidance during placement of intravascular/intracardiac catheters [128–130]. TEE also influences anesthetic management in CHD by guiding changes in inotropic strategy and volume replacement [131,132].

Intraoperative TEE can influence surgical management in 3–15% of cases, including a 3–5% change in the preoperative diagnosis and a return to CPB rate of 3–7% [132–134]. A report on intraoperative TEE during congenital heart surgery in a wide range of patients (2 days to 85 years) described a major impact in 13.8% of the group [135]. The impact was more frequent during reoperations and in those undergoing valve repairs and complex outflow tract reconstructions.

A critical role of intraoperative TEE is the assessment of the adequacy of the surgical intervention and the detection of residual abnormalities that may require immediate revision [22,136–142]. This feature represents a major benefit of intraoperative TEE, as it can positively influence clinical patient outcomes. In return to CPB situations, factors such as the level of inotropic support, loading conditions of the ventricle, and myocardial function can influence the echocardiographic findings, potentially under- or overestimating the hemodynamic severity of the condition. Consequently, decisions regarding return to CPB should be interpreted within this context and in consideration of the overall risk–benefit ratio with appropriate clinical judgment.

Data regarding improvement in clinical outcomes based on intraoperative TEE are limited. In the absence of rigorous scientific data, the experience regarding the contributions of TEE has been so compelling that the technology has been incorporated into clinical practice in many centers, evolving into the standard of care. In a series of 230 patients, if a residual abnormality was detected by TEE and revised, the outcome was improved, and if the patient was left with a residual defect, the outcome was suboptimal [140]. In addition to the patient benefits afforded by this imaging modality, the cost-effectiveness of routine TEE during congenital and pediatric heart surgery has also been shown [143,144].
Cardiac catheterization laboratory

During the past several decades, transcatheter-based therapies and interventional procedures have become increasingly employed in the non-surgical management of congenital cardiovascular anomalies. Many of these approaches have extended from the cardiac catheterization laboratory to the operating room (and vice versa) as combined efforts of interventional cardiologists and cardiothoracic surgeons. TEE allows for safer and more effective application of these interventions by decreasing fluoroscopy time, reducing the amount of contrast material administered, and limiting the duration of the interventional procedure [145]. As with intraoperative TEE, major benefits include acquisition of detailed anatomic and hemodynamic data prior to and during the procedure; real-time evaluation of catheter/device placement across structures; immediate assessment of the results; and monitoring of procedural complications. The high success rate and low incidence of complications with these procedures are a testament to the refinement in interventional techniques coupled with advances in TEE [15].

TEE safety and complications

Although complications related to transesophageal instrumenta- tion have been reported (1–3%), extensive clinical experience indicates that serious complications associated with TEE are rare [148–151]. Probe manipulation can affect hemodynamic and respiratory parameters, requiring attentiveness particularly in small infants [152,153]. Aortic compression can influence blood pressure readings, depending on the location of the arterial monitoring line.

In the patient with an aberrant origin of a subclavian artery with a retroesophageal course, the arterial line should be placed in an extremity not supplied by the anomalous vessel, as loss of the pressure tracing may occur with insertion/manipulation of the TEE probe. This loss occurs because the probe compresses the vessel as it courses behind the esophagus. In fact, occasionally the diagnosis of this vascular anomaly is made upon placement of a TEE probe [154,155]. TEE is of little benefit in the surgical management of isolated vascular anomalies, such as vascular rings, and may in fact be risky, as insertion of a probe can significantly compromise the respiratory function [156]. In infants with anomalous pulmonary venous connections, compression of a posteriorly located pulmonary venous confluence by the TEE probe can cause detrimental hemodynamic effects (Figure 12.12) [46]. If TEE imaging is undertaken in this setting, inserting the probe after sternotomy may be safer [157].

Respiratory compromise can occur from displacement of the ETT or accidental extubation. Capnography can help to identify these complications. If desaturation occurs acutely, the position of the TEE probe tip should be adjusted immediately to neutral and the correct position of the ETT must be confirmed. During removal of the TEE probe, the ETT should be held firmly to avoid inadvertent extubation. Compression of the airways during

Intensive care unit

Echocardiography remains an important diagnostic tool in the ICU to manage postoperative cardiac surgical patients [146]. The presence of bandages, chest tubes, mediastinal air, positive pressure ventilation, and even an open sternum frequently renders TTE imaging difficult. Thus, TEE may be the preferred imaging modality, particularly in ventilated patients, to address an important clinical question [41,147]. In the hemodynamically unstable patient in the ICU, TEE can help to differentiate problems related to preload, myocardial function, afterload, and cardiac tamponade. Localized cardiac compression from a loculated collection or even “dry” tamponade can be diagnosed with TEE in the absence of classic tamponade clinical findings. New findings related to outflow tract obstruction, significant native or prosthetic valve dysfunc- tion, or regional wall motion abnormalities may prompt surgical reintervention. Additional contributions of TEE in this setting include investigation of possible occult shunts and evaluation of mechanical circulatory support devices and assistance during weaning.

KEY POINTS: APPLICATIONS OF TEE IN CHD

- TEE in CHD can be applied in the operating room, cardiac catheterization/electrophysiology laboratory, and critical care setting.
- Preoperative TEE allows for baseline evaluation of anomalies, confirmation of preoperative diagnoses, identification of new or different pathology, exclusion of defects, and refinement of the surgical and anesthetic plans.
- Major roles of postoperative TEE include the assessment of the adequacy of the intervention, guiding the revision of the repair if necessary, and identifying problems associated with weaning from CPB.
- Several factors can influence the echocardiographic findings, potentially under- or overestimating the severity of the condition, warranting their consideration in return to bypass decisions.
- TEE facilitates procedures in the catheterization/electrophysiology laboratory, may enhance their safety, and limits the duration of the intervention.
- TEE is used in the ICU to address important clinical questions when other imaging modalities cannot be used or may not provide the required information, and may define cause in the hemodynamically unstable patient.

TEE is used in the ICU to address important clinical questions when other imaging modalities cannot be used or may not provide the required information, and may define cause in the hemodynamically unstable patient.

- Major roles of postoperative TEE include the assess- ment of the adequacy of the intervention, guiding the revision of the repair if necessary, and identifying problems associated with weaning from CPB.
- Several factors can influence the echocardiographic findings, potentially under- or overestimating the severity of the condition, warranting their consideration in return to bypass decisions.
- TEE facilitates procedures in the catheterization/electrophysiology laboratory, may enhance their safety, and limits the duration of the intervention.
- TEE is used in the ICU to address important clinical questions when other imaging modalities cannot be used or may not provide the required information, and may define cause in the hemodynamically unstable patient.
The clinical manifestations of an ASD are primarily related to the degree of atrial level shunting. The defect size, ventricular compliances, and PA pressures determine the magnitude of the shunt. An ASD, particularly a small defect, may represent an incidental finding on echocardiography. A large defect leading to pulmonary overcirculation results in symptoms of right-sided volume overload. Over time, atrial arrhythmias and heart failure can develop. Although older patients can have evidence
Table 12.6 Pre-and post-cardiopulmonary bypass transesophageal echocardiography (TEE) examination in selected congenital heart defects

<table>
<thead>
<tr>
<th>Condition</th>
<th>Pre-cardiopulmonary bypass</th>
<th>Post-cardiopulmonary bypass</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aortic stenosis</strong></td>
<td>• Define aortic valve anatomy</td>
<td>• Residual outflow obstruction</td>
</tr>
<tr>
<td></td>
<td>• Evaluate location and severity of obstruction (subvalvular, valvular, supravalvular)</td>
<td>• Aortic regurgitation</td>
</tr>
<tr>
<td></td>
<td>• Characterize nature of the pathology</td>
<td>• New VSD</td>
</tr>
<tr>
<td></td>
<td>• Evaluate for aortic regurgitation</td>
<td>• Mitral regurgitation</td>
</tr>
<tr>
<td></td>
<td>• Left ventricular hypertrophy and function</td>
<td>• Ventricular function</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Prosthetic valve function (if applicable)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• If Ross procedure, assess autograft and RV to PA conduit</td>
</tr>
<tr>
<td><strong>Atrial septal defect (ASD)</strong></td>
<td>• Define location and size of defect (defect rims for catheter-based interventions)</td>
<td>All ASD repairs</td>
</tr>
<tr>
<td></td>
<td>• Assess AV valve regurgitation</td>
<td>• Residual shunt</td>
</tr>
<tr>
<td></td>
<td>• Determine RA, RV size</td>
<td>• Ventricular function</td>
</tr>
<tr>
<td></td>
<td>• Baseline ventricular function</td>
<td>• Secondum/primum defects</td>
</tr>
<tr>
<td></td>
<td>• Estimate RVSP (PASP) from TR jet</td>
<td>• AV valve regurgitation</td>
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<tr>
<td></td>
<td>• Presence of associated anomalies</td>
<td>• Sinus venous defect</td>
</tr>
<tr>
<td></td>
<td>– Mitral valve prolapse</td>
<td>• Superior vena cava obstruction</td>
</tr>
<tr>
<td></td>
<td>– Cleft AV valve</td>
<td>• Pulmonary venous obstruction (if associated anomalous pulmonary venous return)</td>
</tr>
<tr>
<td></td>
<td>– Partial anomalous venous drainage</td>
<td></td>
</tr>
<tr>
<td><strong>Atrioventricular septal defect</strong></td>
<td>(AVSD)</td>
<td>All AVSD repairs</td>
</tr>
<tr>
<td></td>
<td>• Define location, size, and type of defects</td>
<td>• Residual shunts</td>
</tr>
<tr>
<td></td>
<td>• Characterize shunting across defects</td>
<td>• Ventricular function</td>
</tr>
<tr>
<td></td>
<td>• Evaluate for additional septal defects</td>
<td>• Partial or ostium primum ASD/cleft mitral valve repair</td>
</tr>
<tr>
<td></td>
<td>• Assess AV valve(s)</td>
<td>• Residual/new AV valve regurgitation (mild regurgitation may be acceptable)</td>
</tr>
<tr>
<td></td>
<td>– Rastelli type in complete defect</td>
<td>• Mitral inflow obstruction (if mitral cleft closed)</td>
</tr>
<tr>
<td></td>
<td>– Relation of valvular structures to ventricles</td>
<td>• Complete AVSD repair</td>
</tr>
<tr>
<td></td>
<td>– Balanced vs. dominant type</td>
<td>• AV valve stenosis (particularly if annuloplasty or left-sided cleft closure is performed)</td>
</tr>
<tr>
<td></td>
<td>– Valvular support apparatus</td>
<td>• AV valve regurgitation</td>
</tr>
<tr>
<td></td>
<td>• Interrogate ventricular outflows (obstruction)</td>
<td>• Left ventricular outflow tract obstruction</td>
</tr>
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<td></td>
<td>• Baseline ventricular function</td>
<td></td>
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<tr>
<td></td>
<td>• Estimate RVSP/PASP</td>
<td></td>
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<tr>
<td><strong>Congenitally corrected</strong></td>
<td></td>
<td></td>
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<tr>
<td>transposition (L-TGA)</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>• Confirm anatomy</td>
<td>AV valve regurgitation</td>
</tr>
<tr>
<td></td>
<td>• Confirm AV and ventriculoarterial relationships</td>
<td>Outflow tracts (for obstruction)</td>
</tr>
<tr>
<td></td>
<td>• Evaluate AV valves</td>
<td>Adequacy of the intervention (pulmonary artery banding, classic repair or double switch operation)</td>
</tr>
<tr>
<td></td>
<td>• Ventricular sizes and function</td>
<td>Evaluate AV valves</td>
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<td>Ventricular function</td>
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<td><strong>Double outlet right ventricle</strong></td>
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<td></td>
<td>• Evaluate septal defects (size, location, shunt direction)</td>
<td>Residual intracardiac shunts</td>
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<td></td>
<td>• Assess relation of VSD to great arteries</td>
<td>Outflow tract obstruction</td>
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<td></td>
<td>• Assess physiology based on anatomic findings (i.e., VSD, transposition or Taussig–Bing, tetralogy type)</td>
<td>AV/semilunar valve regurgitation</td>
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<td></td>
<td>• Great artery relationship (normal, malposed)</td>
<td>LV to Ao baffle (if applicable)</td>
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<td>• Evaluate for outflow obstruction</td>
<td>RV to PA conduit function (if applicable)</td>
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<td></td>
<td>• Ventricular sizes and function</td>
<td>Ventricular function</td>
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<td></td>
<td>• Evaluate associated defects</td>
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<td><strong>Pulmonary stenosis</strong></td>
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<td></td>
<td>• Define pulmonary valve anatomy</td>
<td>Residual outflow obstruction</td>
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<td></td>
<td>• Evaluate location and severity of obstruction (subvalvular, valvular, supravalvular)</td>
<td>Pulmonary regurgitation</td>
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<td></td>
<td>• Characterize nature of the pathology</td>
<td>New VSD</td>
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<td>• Determine size of pulmonary arteries</td>
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<td>• Evaluate for intracardiac shunts</td>
<td>Ventricular function</td>
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<td>• Right ventricular hypertrophy and function</td>
<td>Conduit/prosthetic valve function (if applicable)</td>
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<tr>
<td>Condition</td>
<td>Pre-cardiopulmonary bypass</td>
<td>Post-cardiopulmonary bypass</td>
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<tr>
<td>Tetralogy of Fallot</td>
<td>• Define size and location of septal defects</td>
<td>• Residual VSD</td>
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<td>• Examine for additional VSDs or associated anomalies</td>
<td>• RVOT gradient</td>
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<td>• Evaluate right ventricular outflow tract (subvalvular, valvular, supravalvular regions)</td>
<td>• If residual obstruction, define nature (fixed vs. dynamic) and severity</td>
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<td>– Define morphology, obstruction, gradients</td>
<td>• Pulmonary regurgitation</td>
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<td>• Determine size of pulmonary arteries</td>
<td>• RVSP (from TR jet)</td>
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<td>• Aortic valve competence/aortic override</td>
<td>• Right and left ventricular function</td>
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<td></td>
<td>• Origin and course of coronary arteries</td>
<td>• Conduit/prosthetic valve function (in pulmonary position)</td>
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<td>• Baseline ventricular function</td>
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<td>Transposition of great arteries</td>
<td>• Confirm anatomy and ventriculoarterial relationships</td>
<td>Arterial switch operation (Jatene procedure)</td>
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<tr>
<td>(D-TGA)</td>
<td>• Assess intracardiac shunts (location, size, flow direction, relation to outflows)</td>
<td>• Neoaortic and pulmonary anastomoses (for stenosis)</td>
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<td>• Assess for outflow tract obstruction</td>
<td>• Semilunar valve competence</td>
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<td>• Evaluate AV and semilunar valves</td>
<td>• Outflow tracts (for obstruction)</td>
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<td>• Origin and course of coronary arteries</td>
<td>• AV valve regurgitation</td>
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<td>• Ventricular sizes and function</td>
<td>• Residual intracardiac shunts</td>
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<td>– Assess septal geometry (indicator of ventricular pressures)</td>
<td>• Coronary flow</td>
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<td>Truncus arteriosus</td>
<td>• Septal defects (size, location)</td>
<td>• Global and segmental LV function</td>
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<td>• Truncal valve (for stenosis/regurgitation)</td>
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<td>• Origin of the pulmonary arteries</td>
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<td>• Pulmonary blood flow</td>
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<td>• Ventricular function</td>
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<tr>
<td>Single ventricle</td>
<td>• Evaluate morphologic type</td>
<td>Fontan or Glenn procedure</td>
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<td></td>
<td>• Assess AV and semilunar valves, inflows, and outflows</td>
<td>• Flow in Fontan/Glenn connections</td>
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<td>• Adequacy of interatrial communication</td>
<td>• Evaluate Fontan fenestration, if performed</td>
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<td>• Evaluate prior surgical interventions</td>
<td>• AV valve regurgitation</td>
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<td>• Assess ventricular function</td>
<td>• Residual VSD shunt</td>
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<td>Ventricular septal defect</td>
<td>• Define location and size of defect</td>
<td>• Estimate RVSP (PASP) from TR jet</td>
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<td>(VSD)</td>
<td>• Evaluate for additional intracardiac shunts</td>
<td>• Ventricular function</td>
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<td>• Investigate for associated pathology:</td>
<td>• Regional wall motion (coronary artery)</td>
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<td>– AV valve regurgitation</td>
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<td>• Aortic valve herniation/prolapse</td>
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<td>• Pulmonary valve stenosis</td>
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<td>• Double-chamber RV</td>
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<td>• Baseline ventricular function</td>
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<td>• Estimate RVSP (PASP) from TR jet or VSD peak velocity</td>
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Ao, aorta; AV, atrioventricular; AVSD, atrioventricular septal defect; LV, left ventricle; PA, pulmonary artery; PASP, pulmonary artery systolic pressure; RA, right atrium; RV, right ventricle; RVSP, right ventricular systolic pressure; TR, tricuspid regurgitation.
Figure 12.13 Atrial Septal Defects (ASDs). (A) Secundum ASD. The centrally located septal deficiency in this defect within the region of the fossa ovalis (arrow) and adjacent rims in the interatrial septum (IAS) are readily seen in a mid-esophageal bicaval (ME Bic) view. Comprehensive septal rim assessment requires multiple views. (B) Ostium primum ASD. The inferior communication in the IAS in this defect (arrow) is best seen in a mid-esophageal four-chamber (ME 4 Ch) view. Note insertion of both atrioventricular valves (AVVs) into the interventricular septum (IVS) at the same level. A cleft (commissure) in the anterior mitral valve (MV) leaflet can be visualized in the transgastric basal short-axis (TG basal SAX) view and regurgitation assessed in this and other views of the MV (ME two-chamber [ME 2 Ch], ME mitral commissural [ME MV Comm], ME long-axis [ME LAX]). Mitral valve chordal attachments to the IVS, if present, can be defined in the ME five-chamber (ME 5 Ch), ME LAX, transgastric long-axis (TG LAX), and deep transgastric five-chamber (DTG 5 Ch) views and assessed for related left ventricular (LV) outflow tract obstruction. (Source: Vegas [193] Reproduced with permission of Springer.) (C) Sinus venosus ASD. Optimally imaged in the ME Bic or modified views. Slight probe withdrawal in the ME Bic view images the defect (small arrow) and superior vena cava (SVC) as it enters the right atrium (RA) in the superior defect as shown; advancing the probe to the lower esophageal inferior vena cava (LE IVC) view displays the region where the IVC joins the RA in an inferior defect. Anomalous drainage of the right upper pulmonary vein (RUPV) in the SVC-type defect (long arrow) results from unroofing of the wall that separates the RUPV from the left atrium (LA) as shown here by color Doppler interrogation of pulmonary venous flow. (D) Coronary sinus ASD. The coronary sinus (CS) is best examined in views that display this structure in both its long and short axes. A dilated CS is best imaged by probe retroflexion in the ME 4 Ch view or slight advancement towards the lower esophagus. Unroofing of the CS in this defect is demonstrated by echo dropout in the wall that separates the LA from the CS in the ME (4 Ch, 2 Ch, MV Comm, and LAX) views. Probe angulation between 90° and 120° assisted by color Doppler in a ME Modified Bic view depicts flow from the CS into the RA in the inferior portion of the atrium as shown here. A persistent left SVC, if present, can be demonstrated in the ME MV Comm view as a wedge-shaped echo-free space between the left upper pulmonary vein and left atrial appendage or at the level of the AV junction in the ME 4 Ch and 2 Ch views. RV, right ventricle.
of elevated PASP, severe pulmonary hypertension rarely occurs.

**Highlights of the TEE examination**

Multiple ME views are used to completely assess the relatively thin IAS [165]. The perpendicular alignment of the imaging plane in the ME Bic view images the IAS most reliably. In the ME 4 Ch view, the plane is parallel to the IAS, and hence tissue may appear to be absent from dropout. The size of the atrial communication is measured from the gap in the septal tissue. Communications at the atrial level as displayed by TEE are shown in Figure 12.13.

Abnormal blood flow across the IAS is easily detected by color and spectral Doppler interrogation. Left-to-right shunting is usually the case for an isolated ASD, but it may be right-to-left or bidirectional when co-existent defects are present. The peak velocity across the defect is inversely proportional to the size of the defect, with a larger defect having lower velocity laminar flow. Elevation of PASP is rarely seen in association with ASDs, as noted, but can occur with long-standing shunts. The PASP can be estimated from the peak velocity of the tricuspid regurgitation (TR) jet, if present, as previously discussed. Saline contrast is the most sensitive method to detect interatrial shunts that are not evident by 2D or Doppler techniques. A contrast study is performed by vigorously agitating saline (3–10 mL) with <1 mL of air and injecting it rapidly into a central or arm vein. A negative study represents no flow of bubbles across the IAS. A positive study indicates right-to-left shunting with microbubbles present in the LA within five heartbeats. A false-positive study may occur from pulmonary arteriovenous malformations. Additionally, the presence of negative contrast from non-contrasted blood appearing in the contrast-filled RA can be helpful in identifying left-to-right shunting. Saline contrast increases FFO detection both at rest and with raised RAP [166]. A Valsalva maneuver can enhance the recognition of a small or intermittent right-to-left interatrial shunt. In the intubated patient, a simulated Valsalva maneuver can be performed by sustaining lung inflation to a positive inspiratory pressure of about 25 mmHg for approximately 10 seconds.

The pre-surgical TEE examination for an ASD should confirm location of the defect, its size, and direction of the shunt. Guided by the specific type of defect, the TEE study should consider the presence/potential for MV prolapse (secundum ASD), cleft MV (primum ASD), PAPVD (sinus venosus ASD), and presence of LSVC to coronary sinus connection (coronary sinus ASD). Additional aspects of the TEE study in all defects include evaluation of AV valve competence, associated anomalies, and ventricular function. Atrial communications with significant left-to-right shunting are associated with RA and RV enlargement, and diastolic flattening and paradoxical motion of the interventricular septum (IVS). The post-surgical TEE examination should evaluate the IAS for residual shunting, valvular competence, ventricular function, and nature of flow across the systemic and pulmonary veins, depending on the defect and type of intervention undertaken.

Transcatheter device placement is now widely applied to closure of secundum ASDs [13]. TEE assists in patient selection, procedural guidance, and immediate assessment of success and complications. Defect sizing, determination of location, characterization of orifice (single vs. multiple), evaluation of dimensions and adequacy of septal rims, and assessment of the relationship of the defect to surrounding structures are essential components of the TEE examination and represent an important aspect of decision-making [167–169]. Post-deployment TEE assesses the device (integrity, position, and stability), residual shunt, and presence of complications (Figure 12.14) [13,170]. Surrounding structures can be affected by

![Figure 12.14](image-url)
Figure 12.15 Ventricular septal defects (VSDs). (A) Perimembranous (PM) VSD. The defect is visualized in views that display the tricuspid valve (TV) and/or aortic valve (AoV) at the level of the mid-esophagus, such as the five-chamber (ME 5 Ch), AoV long-axis (ME AoV LAX) (shown), and right ventricular inflow-outflow (ME RV In-Out) views. Associated TV abnormalities may be present (aneurysmal septal tissue partially occluding the VSD), AoV cusp prolapse, or subaortic stenosis requiring additional cross-sections for evaluation. (B) Muscular (Musc) VSD. The defect is examined by performing sweeps of the entire ventricular septum and identifying deficiencies surrounded exclusively by muscle rims. The communication is usually best seen in the ME four-chamber (4 Ch; shown), ME LAX, and transgastric/deep transgastric (TG/DTG) views. Color Doppler may be required to demonstrate small serpiginous or, on occasion, multiple adjacent muscular defects (“Swiss cheese septum”). (C) Outlet VSD. The defect is best seen in views that display the outflow portion of the RV, near the pulmonary valve (PV) and AoV (left panel). The ME RV In-Out view is particularly helpful in determining the type of VSD, as a septal deficiency close to the PV indicates an outlet VSD, in contrast to a PM defect located nearer to the TV valve (right panel). An outlet VSD may potentially distort the AoV, resulting in cusp prolapse (usually of the right coronary cusp) with associated AoV regurgitation. This is optimally examined in the ME AoV LAX view by 2D imaging and color flow mapping. (Source: Vegas [193] Reproduced with permission of Springer.) (D) Inlet VSD. The defect in the superior aspect of the muscular septum is identified in a scan plane (ME 4 Ch view) that shows the region where the atroventricular valves would normally join the interventricular septum (crux of the heart). Inlet defects are located more superiority in the muscular septum than posterior muscular VSDs. Ao aorta; LA left atrium; LV left ventricle; PA pulmonary artery; RA right atrium.
placement of a device, resulting in compromised inflow from the SVC, IVC, coronary sinus, or pulmonary veins, interference with valve function, and pericardial effusion.

**Ventricular septal defects**

**Anatomic and physiologic features**

The ventricular septum is a complex 3D structure formed by morphologically distinct subunits that may have tissue deficiencies creating defects. The categorization of VSDs has been the subject of ongoing debate. For the purpose of this chapter, we will use the classification scheme based on the location of the defect within the ventricular septum as follows: membranous, muscular, inlet, or subarterial.

A perimembranous defect (70% of VSDs), also referred to as membranous, paramembranous, conoventricular, and infracristal defect, involves the thin membranous portion of the IVS adjacent to the TV and AoV. A muscular defect (20% of VSDs) can be found anywhere in the trabecular septum (mid, apical, anterior, and posterior regions) and is bound entirely by muscle. Single or multiple defects can be present. An inlet defect (5% of VSDs), also referred to as “canal type of defect,” results from incomplete formation of the central fibrous body or AV canal septum (see AVSD below). This communication is located at the crux of the heart, adjacent to the MV and TV annuli. An outlet defect (5% of VSDs), also known as infundibular, conal, subpulmonary, supracristal, doubly committed, or subarterial defect, is found in the muscular portion of the septum that separates the outflow tracts. Frequent overlap occurs among the various types of VSD, as they may extend from one primary region to another. Associated lesions, including patent ductus arteriosus (PDA; 6%) and coarctation of the Ao (CoA; 5–10%), can be present.

**Highlights of the TEE examination**

Multiple TEE views are required for systematic interrogation of the entire IVS [171]. Each type of VSD can be identified using 2D imaging (Figure 12.15), although small defects may require superimposed color Doppler to define their location and optimize spectral Doppler alignment. Contrast injection can be helpful if the presence of a defect is suspected but cannot be otherwise demonstrated. In isolated defects, spectral Doppler interrogation shows systolic left-to-right shunting across the ventricular septum, with a peak jet velocity inversely proportional to defect size. A small restrictive VSD is characterized by turbulent color Doppler flow, with a high peak velocity consistent with a ventricular pressure gradient. A large, unrestricted VSD equalizes pressures between the ventricles and elevates PASP. A significant left-to-right shunt causes left-sided volume overload with dilatation of the LA and LV. Eisenmenger syndrome, rarely seen today, results from unrestricted interventricular shunting altering the pulmonary vasculature and, thereby, causing elevated arteriolar resistance with reversal in the shunt direction from left-to-right to right-to-left. Estimation of RVSP (or PASP) can be obtained from the TR or VSD jets.

**Preoperative TEE examination** should, in all cases, confirm the location, size, and number of defects, assess the chamber and PA sizes, and evaluate ventricular function [171]. Spectral Doppler interrogation should determine shunt direction and magnitude, degree of pressure restriction, and estimated PA pressures. The presence of associated cardiac anomalies, valvular competence, and outflow tract obstruction should be assessed. The post-CPB TEE study focuses on evaluation of residual shunting, PASP, and ventricular function [172]. One should consider that a large proportion of residual VSD shunts are trivial.
Atrioventricular septal defects
Anatomic and physiologic features
Atrioventricular septal defects, also known as common AV canal or endocardial cushion defects, are characterized by a defect(s) of the AV septum and abnormalities of the AV valves. A well-known classification scheme proposes that only two categories of AVSDs, the complete and partial forms, should be recognized [174]. However, additional forms have been described, at times leading to confusing nomenclature [175]. The various categories are as follows:

- **Complete defect**, characterized by a single annulus, common AV valve with five leaflets, and contiguous communications at the atrial (primum ASD) and ventricular (inlet VSD) levels
- **Intermediate defect**, described as having a primum ASD, large non-restrictive VSD, and common AV valve annulus separated by a “tongue” of tissue into two valvular orifices
- **Partial defect**, consisting of a primum ASD and cleft in the left or anterior MV leaflet
- **Transitional defect**, having in addition a small inlet VSD due mostly to obliteration by right-sided or TV valve chordal attachments to the ventricular septum.

Complete defects are usually associated with significant intracardiac shunting, resulting in pulmonary overcirculation and left-sided volume overload. Intermediate defects physiologically resemble the complete form of the defect. Partial and transitional defects essentially behave as an ASD. Associated defects in AVSDs include tetralogy of Fallot (TOF), double outlet RV, and total anomalous pulmonary venous drainage or pulmonary atresia in more complex, heterotaxy-type defects.

**Left ventricular outflow obstruction**
Anatomic and physiologic features
Obstruction along the LVOT can occur at the subvalvular, valvular, or supravalvular levels, or may be more distally situated (as in CoA or aortic arch interruption). **Valvular aortic stenosis** can occur in association with a bicuspid AoV (BAV) caused by valve thickening and/or progressive calcification. Coexisting lesions can include PDA, CoA, and other left-sided obstructive pathology. The potential for valvular regurgitation and/or aortic root dilatation from an ascending aortopathy is well recognized with a BAV. **Supravalvular aortic stenosis** arises from a discrete membrane, fibromuscular ring, or muscular tunnel obstruction. Associated lesions include CoA and abnormalities of the MV. **Shone complex** consists of a subaortic membrane, BAV, supravalve mitral ring, and CoA. **Supravalvular aortic stenosis** is characterized by narrowing of the ascending Ao at the sinotubular junction, a pathology that can be seen in children with William syndrome. An obstructive arteriopathy affecting various regions of the Ao, aortic arch vessels, and even the coronary arteries can be found in some cases. The physiological repercussions of any form of left-sided outflow tract obstruction relate to impedance to LV ejection, leading to elevation of systolic pressure, a gradient between the proximal and distal regions across to the obstruction, increased myocardial force, and LV wall stress.

**Highlights of the TEE examination**
Two-dimensional and real-time 3D TEE can adequately characterize anatomy and identify pathology in the outflow tract, AoV, and aortic root [178–182]. Alternate imaging modalities such as MRI and/or CT may be required to more precisely define the anatomy of the Ao and its branches. Regardless of the specific nature of the obstruction, the TEE examination should include assessment of AoV morphology and function, aortic annulus and root size, and the LV to determine size, wall thickness, and function (Figure 12.18). Depending on the type of obstructive pathology, details of relevance in the TEE examination include the presence/severity of associated aortic annular/root hypoplasia, aortic root dilation (post-stenotic or otherwise), and other co-existing lesions. Cross-sections in the mid- and upper esophagus facilitate the examination of the mid-ascending Ao (ME asc Ao LAX and SAX views).

Interventions for LVOT pathology are aimed at alleviating the obstruction and involve a variety of approaches. The TEE examination performed after surgery or catheter-based procedures is directed by the specific intervention but often consists of determination of presence/residual severity of outflow obstruction and AoV competency [140]. After a subaortic resection, it is important to exclude the presence of an iatrogenic VSD or damage to the MV. In the case of autologous PV replacement of a diseased AoV (Ross procedure), relevant aspects of the examination include assessment of graft...
Figure 12.17 Atroventricular septal defect (AVSD). (A) Defects in the atrioventricular (AV) septum. The septal defects (arrows) in a patient with an AVSD (primum atrial septal defect, inlet ventricular septal defect) as displayed in the mid-esophageal four-chamber (ME 4 Ch) view are shown. Additional aspects of the evaluation should include determination of shunt flow by color Doppler, morphology and function of valvular structures, and ventricular size and function. (B) Subaortic stenosis. Subaortic obstruction caused by atroventricular valve (AVV) attachments to the interventricular septum or elongation of the left ventricular outflow tract (LVOT) from inlet-outlet disproportion may be evident by two-dimensional imaging and color/spectral Doppler interrogation in views that display the LVOT (ME five-chamber [ME 5 Ch], ME aortic valve long-axis [ME AoV LAX] as shown, transgastric long-axis [TG LAX], and deep transgastric five-chamber [DTG 5 Ch]). (C) Left AVV cleft. A cleft in the left AVV can be clearly displayed using en face views by three-dimensional transesophageal echocardiography. Superimposed color Doppler allows for characterization of associated regurgitant jets. (D) Post-cardiopulmonary bypass examination. The post-repair evaluation includes assessment of AVV function to exclude significant regurgitation or stenosis and the presence of residual intracardiac shunts. The ME 4 Ch image shown depicts a tiny left ventricular (LV) to right atrial (RA) shunt and a trivial amount of regurgitation at the septal aspect of the left AVV (base of the cleft). Ao, aorta; LA, left atrium; RV, right ventricle.
Figure 12.18  Left ventricular outflow obstruction (LVOT). (A) Valvular aortic stenosis. In aortic valve (AoV) stenosis, the number and mobility of the valve cusps, and the qualitative severity of the obstruction are best appreciated in the mid-esophageal AoV short-axis (ME AoV SAX) and long-axis (ME AoV LAX) views. A systolic frame of a functionally bicuspid valve is depicted in this ME AoV SAX image; note the presence of commissural fusion. (B) Subaortic stenosis. Two-dimensional (2D) and color Doppler interrogation of a fibromuscular membrane (arrows) causing subaortic stenosis in the ME AoV LAX view. This cross-section, in addition to the ME five-chamber (ME 5 Ch), transgastric LAX (TG LAX), and deep transgastric 5 Ch (DTG 5 Ch) views, are essential in defining the level and nature of the obstruction in any of the lesions that affect the LVOT. Superimposed color Doppler demonstrates turbulence at the level of the obstruction (as shown) and also provides for evaluation of AoV function. Continuous-wave Doppler interrogation in the TG and DTG views allows for determination of the pressure gradient across the region, whereas pulsed-wave Doppler defines the level of obstruction. Abnormal AoV systolic closure and/or fluttering of the valvular cusps, if present, are best seen in the ME AoV SAX and LAX views. (Source: Vegas et al. [33]. Reproduced with permission of Springer.) (C) Supravalvular aortic stenosis. The typical hourglass deformity (arrows) at the Ao sinotubular junction is displayed in the ME AoV LAX view (as shown) by 2D imaging and color-flow Doppler (note the site of color aliasing). Dilation of the coronary arteries may result from exposure to high left ventricle (LV) pressures (best seen in the ME AoV SAX and LAX views with multiplane angle adjustments). The potential for myocardial ischemia from compromised coronary blood flow in this lesion can manifest on transesophageal echocardiography as segmental wall motion abnormalities and requires a combination of views that display the various regions of the ventricles (refer to Figure 12.11). Ao, aorta; LA, left atrium; RA, right atrium.
function (autograft and PV allograft) and segmental wall motion analysis as a surrogate for complications related to coronary re-implantation. Evaluation of prosthetic valve function and the exclusion of paravalvular leak(s) are essential following AoV replacement.

**Right ventricular outflow obstruction**

**Anatomic and physiologic features**

As in the case of LVOT obstructive lesions, those that affect the RVOT may be confined to the subvalvular, valvular, or supravalvular levels, or concomitantly involve multiple regions. Pulmonary (pulmonic) valve stenosis (PS) represents the most common lesion. It is characterized by thickening or fusion of the leaflets resulting in valvular narrowing. The variable size of the valvular orifice accounts for the severity of the obstruction. Less frequently, the stenosis can be caused by valvular dysplasia. Associated defects include an ASD, VSD, and obstructive subpulmonic hypertrophy.

Right ventricular outflow tract obstruction results in an elevated RV systolic pressure and wall hypertrophy, proportional to the degree of obstruction. Severe pressure loads can, in some cases, result in RV dilatation and failure.

**Highlights of the TEE examination**

The malformation that causes severe valvular PS is best examined in the ME RV In-Out, ME asc Ao SAX, and UE Ao Arch SAX views (Figure 12.19). Typical findings include valvular doming and reduced systolic leaflet excursion. Color Doppler shows turbulent antegrade flow at the level of the valve, and, depending on associated pathology, adjacent sub-or supravalvular regions [183]. Pulmonary regurgitation can also be present. Pulsed-wave Doppler can establish the level and continuous-wave Doppler can determine the peak pressure gradient across the obstruction. Modified TG views may permit better Doppler alignment, particularly if UE views are unobtainable. The estimation of RV systolic pressure using the peak velocity of the TR jet provides another parameter to determine the severity of the obstruction. Severe PS is associated with RV hypertrophy, as can be detected in the ME 4 Ch and ME RV In-Out views and in views that display the RV in the TG and DTG windows. Systolic IVS flattening is present in most cases of severe valve obstruction with preserved RV function. Post-stenotic dilatation of the main PA may be present.

In most cases, isolated valvular PS can be managed by catheter interventions. Real-time 3D TEE has been demonstrated to enhance monitoring during percutaneous valvuloplasty [184]. In patients requiring surgery for pathology that affects the valve itself, adjacent regions or multiple levels, following relief of the obstruction, the post-CPB TEE examines the residual outflow pressure gradient, presence and severity of pulmonary regurgitation, identifies new pathology (VSD, TR), and assesses biventricular function. Additional applications of TEE are guided by the need to address associated lesions.

**Tetralogy of Fallot**

**Anatomic and physiologic features**

In the classic lesion, the four components of TOF consist of a large VSD, RVOT obstruction, aortic override, and RV hypertrophy. The diverse clinical manifestations in this lesion relate to the variable anatomic features, particularly the severity of the RVOT obstruction. Associated pathology includes an atrial level communication (PFO or ASD), additional VSDs, an LSVC to coronary sinus connection, coronary artery anomalies, and variants of aortic arch sidedness/branching pattern. Concomitant lesions such as an AVSD (colloquially referred to as “tet-channel” defect) can be present in some cases. Pulmonary atresia with a VSD represents a severe form of disease in TOF.

**Highlights of the TEE examination**

The abnormalities that comprise the TOF spectrum are easily identifiable by TEE (Figure 12.20) [185]. The TEE examination requires detailed interrogation of the RVOT, main and proximal branch PAs, particularly from UE and ME levels. Spectral and color Doppler are essential for determining the level and severity of the obstruction. The ventricular septum is examined in multiple views that display the VSD and exclude additional communications at the ventricular level. Right ventricular size, chamber hypertrophy, and function can be assessed from the ME 4 Ch, TG, and DTG views. Additional TEE planes of interrogation are needed for the assessment of associated defects.

*Postoperative TEE* after complete repair of TOF evaluates for residual RVOT obstruction, PV competence, VSD patch leak(s), and ventricular function [73,186–188]. Patients who have undergone TOF repair in infancy/childhood present most often in late adolescence or adulthood with pulmonary regurgitation and the effects of chronic volume overload to the right heart. In some cases, the RV, and even the LV, may display systolic impairment. The presence of residual RVOT obstruction and intracardiac shunts should be explored using similar TEE views as those applied in the evaluation of the uncorrected lesion.

**Double outlet right ventricle**

**Anatomic and physiologic features**

A VA connection in which both great arteries are nearly or completely aligned to the RV is referred to as a DORV. The exact diagnostic criteria for DORV are controversial. It does not represent a single disease but rather a spectrum of pathologies, and it may share features with other lesions such as TOF and transposition. A VSD is almost always present. The location of the VSD and its relation to the great vessels play a critical role in the physiology and can be described as subaortic (commonest), subpulmonary (i.e., Taussig–Bing anomaly), doubly committed, or non-committed (remote). The spatial orientation of the great vessels is frequently abnormal and can be side-by-side or in the configuration of D-transposition of the great arteries (D-TGA). The physiologic manifestations
Figure 12.19  Right ventricular outflow obstruction (RVOT). (A) Valvular pulmonary stenosis (PS). Stenosis of the pulmonary valve (PV) can be due to valvular thickening, commissural fusion, and/or valvular dysplasia. The malformation is best examined in the mid-esophageal right ventricular inflow-outflow (ME RV In-Out), ME ascending aortic short-axis (ME asc Ao SAX), and upper esophageal aortic arch short-axis (UE Ao Arch SAX) views. Typical findings include valvular doming and reduced systolic leaflet excursion. The ME asc Ao SAX zoom view shown depicts a thickened PV and associated post-stenotic dilation of the main pulmonary artery (PA) in a patient with valvular stenosis. (B) Subvalvular PS. Muscular hypertrophy of the subvalvular pulmonary region can occur in isolation or may be present in association with valvular PS. The narrowing can be of a fixed or dynamic nature. The ME RV In-Out image shown displays severe subvalvular narrowing. (C) Supravalvular PS. Discreet narrowing of the supravalvular region is occasionally seen in association with valvular PS or the pathology can be found in isolation. This is best examined in views that display the pulmonary outflow tract in its long-axis, as shown in a ME Modified RV In-Out view. (D) Estimation of right ventricular systolic pressure (RVSP). Moderate to severe RVOT obstruction is frequently associated with some degree of tricuspid regurgitation (TR). The peak velocity of the TR jet, as shown, allows for estimation of the RVSP, providing another parameter to assess the severity of the outflow obstruction. In this example, the RVSP, as derived from the simplified Bernoulli equation, is \( \sim 48 \text{ mmHg} \left( (3.09)^2 + \text{right atrial (RA) pressure (assumed 10 mmHg)} \right) \). The RVSP in this case does not reflect the pulmonary artery systolic pressure (PASP) as this is determined by the equation: PASP = RVSP – PV pressure gradient. (E) Spectral Doppler. Interrogation using spectral Doppler from the deep transgastric (DTG) sagittal view depicts the late systolic, “dagger-shaped” signal, that characterizes dynamic RVOT obstruction. (F) Continuous-wave (CW) Doppler. The image depicts the optimal alignment for spectral Doppler interrogation that can be obtained from DTG imaging. In this example, CW was used to obtain the peak systolic pressure gradient between the right ventricle (RV) and PA (58 mmHg) and assess the severity of the RVOT obstruction. LA, left atrium; LV, left ventricle.
Figure 12.20 Tetralogy of Fallot (TOF). (A) Conoventricular ventricular septal defect (VSD). The large VSD in TOF is optimally seen in the mid-esophageal long-axis (ME LAX; shown), ME five-chamber (ME 5 Ch), ME right ventricular inflow-outflow (ME RV In-Out; panel B), and transgastric/deep transgastric (TG/DTG) views. These same views display the aortic (Ao) override over the VSD. Color Doppler facilitates assessment of defect size and direction of shunting. (B) Right ventricular outflow tract (RVOT) obstruction. The RVOT (subvalvular, valvular, and supravalvular areas) is best evaluated in the ME RV In-Out view. The typical anterior and leftward deviation of the conal or infundibular septum that causes subpulmonary muscular dynamic obstruction, as well as the VSD, can be optimally displayed in this view as shown. (C) Pulmonary regurgitation. Transannular patch repair in TOF resulting in pulmonary regurgitation is best evaluated in views that display the RVOT in long-axis as shown. Note the blue color Doppler jet representing flow into the RV during diastole and the to-and-fro flow across the RVOT by spectral Doppler. (D) VSD patch leak. Assessment of residual ventricular level shunting is an important component of the post-repair transesophageal echocardiographic examination after corrective surgery and during subsequent reoperations in TOF. The ME aortic valve long-axis (ME AoV LAX) view shown here demonstrates a small VSD patch leak by color Doppler and associated high-velocity left-to-right shunting by spectral Doppler. LA, left atrium; LV, left ventricle; PA, pulmonary artery; RA, right atrium. Heart diagram courtesy of Ms. Willa Bradshaw.

are variable and may mimic those of an isolated VSD, TOF, D-TGA, or single ventricle. The heterogeneous nature of the lesion requires careful preoperative assessment and surgical planning.

**Highlights of the TEE examination**

**Preoperative TEE** evaluates the location and size of the VSD and its relationship to the great arteries (Figure 12.21). The spectral and color Doppler modalities are important in the assessment of flow out of the LV and across the VSD when the defect is subaortic in location. These modalities are essential in the evaluation of the severity of associated outflow tract obstruction (right and left) and valvular function (stenosis or regurgitation).

In most instances for which a biventricular repair is feasible, surgery aims to restore normal anatomy.
Figure 12.21  Double outlet right ventricle (DORV). (A) Subaortic ventricular septal defect (VSD). Mid-esophageal five-chamber (ME 5 Ch) view depicting the most common variant of DORV with a malalignment VSD in subaortic location (left panel). Note the ventricular communication (arrow), the abnormal relationship of the aorta (Ao) to the right ventricle (RV), and the presence of muscular conus resulting in mitro-aortic discontinuity. Color and spectral Doppler in the ME views (four-chamber, 5 Ch, long-axis [LAX]) determine the direction and pattern of shunting across the VSD. The unusual pathway of blood flow from the left ventricle (LV) to the Ao, as shown by color Doppler (right panel), represents a substrate for potential subaortic stenosis after the repair. (B) Subpulmonary VSD. Deep transgastric five-chamber (DTG 5 Ch) view in Taussig–Bing anomaly depicting the relationship of the great arteries to the RV in this defect and the subpulmonary location of the VSD accounting for preferential flow of LV blood into the pulmonary artery (PA) and the physiology of D-transposition of the great arteries. (C) Side-by-side great arteries. The abnormal side-by-side spatial orientation of the great arteries in DORV (patient with a subaortic VSD) is seen in these zoom two-dimensional and color Doppler images. This relationship is in contrast to their criss-cross orientation in the normal heart. (D) VSD flow. ME LAX view in same patient as in C with DORV depicting the relationship of the VSD to the Ao and evaluation of VSD flow by color Doppler. LA, left atrium; RA, right atrium. Heart diagram courtesy of Ms. Willa Bradshaw.

by establishing continuity between the ventricles and corresponding great arteries using various surgical techniques. In cases in which pulmonary stenosis is present, distinguishing this anomaly from TOF is important. Although the physiology of the two lesions is similar, the presence of a subaortic conus in the patient with TOF-like DORV represents a substrate for subaortic stenosis following the repair, a rare occurrence in TOF. This potential problem should be explored in all TEE views that display the pathway of the blood flow between the LV and Ao (ME 5 Ch, ME LAX, TG LAX, DTG 5 Ch). In addition, post-repair TEE, depending on the details of the anatomy and nature of the intervention, should exclude residual intracardiac shunting, evaluate for any other forms of outflow tract obstruction and valvular regurgitation, and assess ventricular function.

Transposition of the great arteries
Anatomic and physiologic features
In D-TGA, concordance in the AV connections and discordance in the VA connections are present. The segmental anatomy in most cases is that of [S,D,D], meaning normal visceroatrial arrangement or visceroatrial situs solitus (S), D-loop ventricles (D), and D-transposition of the great arteries. In contrast to the normal heart, in which the Ao is posterior and rightwards of the anterior and leftwards PA, in this arrangement the Ao originates from the RV anteriorly and to the right of the posterior and leftwards PA. The physiology is characterized by separate parallel circulations. A communication, usually an ASD or PDA, is essential for intercirculatory mixing and allows partially oxygenated blood to reach the systemic circulation. In most cases, the ventricular septum is intact, but VSD(s)
of various sizes can be present. Associated findings can include pulmonary outflow obstruction, coronary artery variants, and aortic arch anomalies.

**Highlights of the TEE examination**

The TEE evaluation in the patient with D-TGA requires proper 2D identification of cardiac chambers and connections (Figure 12.22). Additional indispensable TEE information includes confirmation of the segmental veno-atrial connections (LE views: Situs SAX and IVC LAX); evaluation of AV valves, ventricular septum, and ventricular function (ME views: 4 Ch, 5 Ch, LAX; TG views: basal, mid SAX, apical SAX); assessment of the LVOT and PV (ME views: LAX, 5 Ch; TG LAX; DTG 5 Ch); and interrogation of the IAS (ME 4 Ch and ME Bic). In addition to the 2D evaluation, the examination should include interrogation of the outflow tracts for obstruction, semilunar valves for stenosis or regurgitation, and origin of the coronary arteries. A comprehensive assessment of the aortic arch may not be feasible with TEE, but a combination of views at the UE and ME levels may allow for limited interrogation.

Surgical correction of D-TGA aims to restore the proper sequence of blood flow. The arterial switch operation (ASO), which allows for anatomic correction by restoring the normal VA relationships, is the favored surgical approach today. It involves transecting the great arteries, anastomosing them to their respective appropriate ventricles, and translocating the coronary arteries. TEE can demonstrate immediate complications after the ASO, including anastomotic site stenosis causing supravalvular obstruction in the PA or Ao [189]; ASD or VSD patch leaks; valve regurgitation; and ventricular dysfunction [189]. Coronary complications should be suspected if global systolic function is impaired or segmental wall motion abnormalities are present [100,101]. The atrial
Figure 12.23 D-transposition of the great arteries (D-TGA) post-Senning and post-Rastelli operations. (A) D-TGA after Senning procedure.
Transesophageal echocardiography (TEE) assessment of atrial pathways is complicated and requires multiple views and sweeps between several planes to trace the flows of blood and provide information about atrial anatomy and the presence of baffle pathology (leak or obstruction). The mid-esophageal modified four-chamber (ME Modified 4 Ch) view (left panel) depicts the systemic venous atrium (SVA), which receives the systemic veins (not shown), and the region of the pulmonary venous atrium (PVA 1) where the pulmonary veins drain. Note the portion of the baffle that separates the SVA from the PVA 1. As the TEE probe shaft is turned rightwards (right panel), the pathway of pulmonary venous flow can be examined to exclude obstruction (from PVA 1 to PVA 2). In patients who have undergone atrial baffle procedures, these views in combination with additional TEE cross-sections assist in the assessment of systemic right ventricle (RV) function, grading severity of tricuspid regurgitation (TR), and the evaluation of potential intracardiac thrombus related to rhythm abnormalities or pacing leads. (B) D-TGA post-Rastelli operation. In the patient with D-TGA and associated ventricular septal defect (VSD) and pulmonary stenosis (PS), a Rastelli-type repair may be favored, where the left ventricle (LV) output is re-routed to the aorta (Ao) across a VSD patch that serves as a baffle, and an extracardiac conduit is placed between the RV and pulmonary artery (PA). The transgastric RV inflow (TG RV In; left panel) and upper esophageal aortic arch short-axis (UE Ao Arch SAX; right panel) views, as shown, are particularly helpful in the examination of the conduit. A combination of TEE modalities that include two-dimensional, color, and spectral Doppler in multiple views can assess outflow obstruction, conduit/aortic regurgitation, residual VSD, and estimate RV systolic pressure in the postoperative patient. MPA, main pulmonary artery; RA, right atrium. Heart diagrams courtesy of Ms. Willa Bradshaw.
switch operation (Mustard/Senning procedures) provided physiologic correction by using intra-atrial baffles to allow deoxygenated blood to reach the PAs and oxygenated blood to be ejected into the Ao (Figure 12.23). It is no longer the surgical intervention of choice because it left the morphologic RV as the systemic pump for life. Patients with this procedure are mostly CHD survivors to adulthood. In patients with prior Rastelli type operations, in which the LV output is routed to the Ao across a baffle and a RV to PA conduit is placed, color and spectral Doppler can assess outflow obstruction, pulmonary/aortic regurgitation, and residual VSD, and estimate PASP.

**Congenitally corrected transposition of the great arteries**  
**Anatomic and physiologic features**

In CCTGA, also referred to as physiologically corrected transposition, the AV and VA connections are both discordant (double discordance). The ventricles and great vessels are malpositioned, meaning the ventricles are inverted and the great arteries are transposed. Although variable, in most cases the anatomy is characterized by levocardia, viscerotracheal situs solitus (S), with systemic veins draining into a right-sided RA connected to a right-sided morphologic LV that ejects across a rightwards and posterior PA; the pulmonary veins drain into a left-sided LA, connected to a left-sided morphologic RV (L-ventricular loop) that ejects across a leftwards and anterior Ao (L-positioned great arteries). This segmental anatomy is referred to as [S,L,L] and frequently, just as L-TGA. In this malformation, the morphologic LV represents the venous, pulmonary ventricle, and the morphologic RV functions as the arterial, systemic ventricle. The physiology is referred to as corrected because desaturated blood reaches the pulmonary circulation and saturated blood enters the systemic circulation. Associated anomalies can include a VSD, pulmonary stenosis or obstruction to morphologic

![Diagram of Congenitally corrected transposition (CCTGA)](image-url)

**Figure 12.24** Congenitally corrected transposition (CCTGA). (A) Ventriculoarterial (VA) discordance (left ventricle [LV] to pulmonary artery [PA] connection). The deep transgastric (DTG) views are essential in the transesophageal echocardiographic (TEE) evaluation of CCTGA (also referred to as L-transposition of the great arteries [L-TGA]). The examination requires not only single views but sweeps between planes to assess ventricular morphology, their arrangement, and connections between these and the arterial trunks. From the deep transgastric (DTG) view shown, the discordant connection between the smooth-walled LV and PA is seen. (B) VA discordance (right ventricle [RV] to aorta [Ao] connection). The view from the DTG window in the same patient depicted in panel A (as the probe is angulated anteriorly) displays the origin of the Ao from the trabeculated left-sided RV. The smooth-walled LV is seen to the right of the morphologic RV. (C) Atrioventricular (AV) discordance. The evaluation of ventricular morphology and AV connections in CCTGA requires imaging in multiple views at the mid-esophageal, transgastric, and DTG levels. As displayed in this ME four-chamber (4 Ch) image, the discordant AV connections are evident as the left atrium (LA) opens into a chamber of RV morphology and the right atrium (RA) drains into the LV. The RV is identified by its trabeculated endocardial surface, the presence of a moderator band, and a septophilic tricuspid valve (TV) that is more apically displaced on the interventricular septum relative to the mitral valve (MV). The subpulmonary ventricle displays a smooth surface and two papillary muscles. Various cross-sections allow for examination of the RV, which often dilates and functions poorly over time, resulting in TV regurgitation. (Source: Vegas [193] Reproduced with permission of Springer.) (D) Orientation of the great arteries. The parallel orientation of the great arteries, with the Ao more anterior, is confirmed in cross-sections that display the outflow tracts in their long axes (ME long-axis [LAX], ME five-chamber [5 Ch], and DTG 5 Ch). The ME LAX image shows this parallel orientation. Note associated pulmonary stenosis (small posterior valvar annulus, stenotic dome leaflets) and the presence of a ventricular septal defect in this case. (E) Co-planar semilunar valves. This lesion makes the aortic valve (AoV) and pulmonic valve (PV) appear co-planar (both valves in their short axes seen at the same level), with the PA spatially positioned posteriorly and to the right (in the center of the image), relative to the anterior and leftward Ao. This abnormal orientation is best seen in the ME aortic valve short-axes (ME AoV SAX; shown), ME ascending aortic short-axis (ME asc Ao SAX), and ME right ventricular inflow-outflow (ME RV In-Out) views. In this example, the PV appears to have possible commissural fusion. Heart diagram courtesy of Ms. Willa Bradshaw.
LV outflow, and abnormalities of the TV (Ebstein-like anomaly and others). The patient with CCTGA may present late in adulthood with TR and systemic RV failure or complete heart block.

**Highlights of the TEE examination**

Diagnosis of CCTGA relies on the accurate identification of cardiac chamber morphology (Table 12.3 and Figure 12.24). In addition to confirmation of the anatomy, an important role of TEE in this defect is the assessment of TV competence (systemic atrioventricular valve), the evaluation of associated defects, and determination of the functional status of the RV.

Depending on the particular type of surgical intervention for this lesion (conduits, baffles, switches), TEE assists in the post-CPB assessment by excluding hemodynamically significant residual lesions that may necessitate revision and evaluating AV and semilunar valve competence, outflow tract obstruction, and ventricular function.

**Truncus arteriosus**

**Anatomic and physiologic features**

Truncus arteriosus refers to the anomaly that has a single arterial trunk from which both the PA and Ao (with coronary arteries) originate. Both ventricles have a single, common outlet and the truncal root overrides a VSD. Hypoxemia results from complete admixture of deoxygenated and oxygenated blood. Classification of this defect into three types (I, II, and III) is based on the origin of the PAs from the truncal root. The clinical manifestations of this lesion depend largely on the status of the pulmonary vascular resistance and the presence of any intrinsic stenosis in the PAs. Associated findings include truncal valve anomalies, right aortic arch, interrupted aortic arch, and coronary ostial anomalies.

**Highlights of the TEE examination**

The common arterial trunk is characterized by the presence of a single semilunar valve; it can have variable cusp number/morphology and can be stenotic or regurgitant (Figure 12.25). A comprehensive pre-CPB TEE examination includes the assessment of truncal valve function and other co-existent lesions.

Corrective surgery for this lesion involves closing the VSD and detaching the main PA segment or individual branches from the truncal root. In most cases, a conduit is placed between the RV and PA. Truncal valve interventions may be required during the initial surgery or subsequently. Post-CPB TEE excludes residual VSD shunting and assesses the function of the truncal valve, RV to PA conduit, and both ventricles. Coronary artery perfusion can be compromised pre- and postoperatively, resulting in global or regional wall motion abnormalities. The RV may dilate and underperform in the face of increased PASP as assessed from estimates of RVSP. In the long-term issues associated with conduit stenosis or regurgitation or truncal valve problems may lead to reoperation. The role of TEE in this setting, in addition to assessing the specifics of the intervention, is similar to that described immediately after the initial corrective procedure.

**Single ventricle**

**Anatomic and physiologic features**

The single ventricle (univentricular heart) spectrum comprises lesions with an atretic AV valve (MV or TV), hypoplastic ventricle (hypoplastic left heart syndrome,
Figure 12.25 Truncus arteriosus (TA). (A) Truncal root. The origin and proximal course of the pulmonary arteries (PAs) from the arterial trunk can be defined by two-dimensional (2D) imaging and color Doppler by adjusting the probe position in the mid-esophageal ascending aortic short-axis and long-axis (ME asc Ao SAX and LAX [shown]) and modified upper esophageal views. (B) Single outlet. The assessment of this lesion requires a combination of planes that display the truncal root in short and long axes (ME aortic valve short [SAX] and long-axis [LAX], and deep transgastric [DTG] views). These same cross-sections provide for assessment of the ventricular septal defect and evaluation of shunting by color and spectral Doppler. Characteristically a single outlet is identified as displayed in this DTG five-chamber (DTG 5 Ch) view, similar to findings in tetralogy of Fallot-pulmonary atresia (note the “adult” orientation of this image with the ventricular apex at the top and outflow at the bottom). (C) Truncal valve. The evaluation of truncal valve morphology and presence/severity of stenosis and/or regurgitation are important components of the examination. In some cases, a quadricuspid truncal valve is present, as can be seen in this ME AoV SAX view. Ao, aorta; LA, left atrium; LV, left ventricle; MPA, main pulmonary artery; RA, right atrium; RV, right ventricle. Heart diagram courtesy of Ms. Willa Bradshaw.

double-inlet LV), or others for which physiologically a biventricular repair is not feasible or desirable (i.e., functional single ventricle). Frequently, this broad group of lesions is characterized by complete admixture of systemic and pulmonary venous blood at the atrial and/or ventricular level. Another common finding is systemic or pulmonary outflow obstruction.

**Highlights of the TEE examination**

A complete and systematic TEE examination should be the goal in all cases; however, considering the many defects that fit into the single ventricle category, the evaluation should be directed at the particular structural abnormalities and associated hemodynamic and functional alterations. Although rarely diagnostic, an essential aspect of the examination is the inclusion of views that confirm the anatomic abnormalities. Occasionally, this interrogation reveals new findings and/or modifies previous ones. Depending on the morphologic substrate, the TEE examination should demonstrate the anatomic/functional features that merit a single ventricle management strategy, such as a hypoplastic ventricle with an atretic or severely stenotic inflow and/or outflow, or a single (common or rudimentary) ventricle with two separate atria that may communicate through an ASD (Figure 12.26). The often enlarged single ventricle may be identified as having right, left, or indeterminate morphology. Most of these features can be evaluated at the level of the mid-esophagus. An initial useful cross-section is the ME 4 Ch view, which serves as a reference point from which the multiplane angle can be adjusted as required for optimal visualization of the various structures of interest. In the setting in which a patient with a two-ventricle heart is not able to undergo surgery that allows for a biventricular repair and where a
Figure 12.26 Single-ventricle variants. (A) Hypoplastic left heart syndrome (HLHS). Deep transgastric five-chamber (DTG 5 Ch) view showing the characteristic features of HLHS. Note the non-existent left ventricular (LV) cavity, small mitral valve (MV), and tiny left atrium (LA). An atrial communication is also seen. (B) Tricuspid atresia. Mid-esophageal four-chamber (ME 4 Ch) view displaying the atretic valve in tricuspid atresia and a hypoplastic right ventricle (RV). (Source for panel B: Motta and Miller-Hance [194] with permission.) (C) Double inlet left ventricle (DILV). ME 4 Ch view depicting two atrioventricular valves opening into a large ventricular chamber, consistent with the diagnosis of DILV. Ao, aorta; PA, pulmonary artery; RA, right atrium; RV, right ventricle. Heart diagrams courtesy of Ms. Willa Bradshaw.
Figure 12.27 Modifications of the Fontan procedure. (A) Classic atriopulmonary connection. Left panel: mid-esophageal four-chamber (ME 4 Ch) view in adult patient with atriopulmonary Fontan connection for tricuspid atresia depicting a large thrombus along the free wall of the right atrium (RA; arrow). Note RA dilation and bulging of the interatrial septum towards to left atrium (LA). Right panel: ME two-chamber view in the same patient showing a dilated coronary sinus due to high RA pressures. (B) Lateral tunnel Fontan connection. Left panel: zoom ME 4 Ch two-dimensional view of a lateral tunnel Fontan connection (circular structure) in the atrium. Right panel: corresponding color Doppler image depicting right-to-left shunting at the level of a Fontan fenestration (arrow). By allowing for venous blood to enter the common atrium, the fenestration maintains cardiac output at the expense of arterial desaturation. (C) Extracardiac Fontan connection. Left panel: ME 4 Ch view showing the extracardiac conduit (arrow) that allows for inferior vena cava blood to enter the pulmonary artery (PA) in an extracardiac Fontan connection. Right panel: as the transesophageal echocardiography probe is rotated rightwards, the Fontan conduit can be further displayed longitudinally in a zoom image. Obstruction to flow of the right-sided pulmonary veins, related to the conduit, should be excluded after Fontan completion. Ao, aorta; LV, left ventricle; RV, right ventricle; SVC, superior vena cava. Heart diagrams courtesy of Ms. Willa Bradshaw.
single-ventricle management strategy is undertaken, the features of the anatomy leading to this approach should be demonstrated.

The evaluation of ventricular morphology, size, and function in single-ventricle variants and two-ventricle hearts not amenable to a biventricular repair is facilitated by 2D imaging in the ME 4 Ch and ME 2 Ch views, and cross-sections obtained at the TG and DTG levels. Assessment of the AV valves examines for their presence (single, double, or common), relationship to the ventricles (straddling and override), patency and functionality (stenosis or regurgitation). This interrogation is best performed at the ME (4 Ch, 2 Ch, RV In-Out, and Mod Bic TV) and TG (RV In) levels. Evaluation of the outflows examines the relation between the ventricles and arterial roots, their patency, and the semilunar valves. This assessment requires multiple views and sweeps obtained at the ME (5 Ch, LAX, AoV LAX, AoV SAX, aso Ao SAX), TG (LAX, RV In-Out), and DTG (5 Ch and modified views) levels. Adequacy of systemic/pulmonary venous admixture or drainage (ME 4 Ch, ME Bic views) should also be established. This comprehensive evaluation in the single-ventricle patient requires the use all available Doppler modalities.

KEY POINTS: EVALUATION OF SELECTED CONGENITAL HEART DEFECTS BY TEE

- The TEE evaluation of CHD assumes an understanding of the anatomic abnormalities and physiologic repercussions of the various defects.
- The review of information obtained in all prior diagnostic studies, but in particular the TTE findings, is critical prior to undertaking TEE.
- The comprehensive TEE evaluation in CHD requires the use of all modalities that include 2D, and in selected cases, possibly real-time 3D imaging, spectral Doppler, and color-flow interrogation.
- The examination assumes the use of multiple TEE planes from all available windows.
- The intraoperative assessment of any defect aims to characterize the abnormalities in question, assess severity of the disease, and evaluate functional aspects related to the AV valves, semilunar valves, and myocardium, which may impact the clinical course.

Single-ventricle surgical management often requires sequential palliative stages. Depending on the anatomy, stage I palliation may consist of a surgical technique aimed at providing for or improving systemic (e.g., Norwood procedure) or pulmonary blood flow (e.g., systemic to pulmonary shunt) or limiting pulmonary overcirculation (i.e., PA banding) in order to balance pulmonary and systemic blood flow. The preoperative TEE examination in this setting confirms the anatomy by evaluating the AV and VA connections; AV valve morphology and function; degree of outflow tract obstruction; size, morphology, and function of the ventricle; and adequacy of the interatrial communication. The post-CPB TEE examines the adequacy of the specific intervention, AV valve competence, and ventricular function. Stage II palliation usually consists of a bidirectional superior cavopulmonary connection (Glenn shunt or hemi-Fontan procedure). Postoperative TEE evaluates patency of the anastomosis, AV valve competence, and ventricular function. The last step or the stage III operation is the Fontan procedure or total cavopulmonary connection using either an intracardiac lateral tunnel or an extracardiac conduit to route IVC blood into the PA (Figure 12.27). In some cases, a fenestration is created to allow blood from the venous system to enter the systemic circulation and maintain cardiac output without depending on passage through the pulmonary circulation. In addition to the anatomic and functional assessment previously mentioned for earlier palliative stages, the post-CPB TEE evaluates the Fontan circuit for obstruction, leaks, and patency of fenestration if present [190,191]. Low-velocity phasic flows should be documented into the PAs and across the IVC/hepatic veins. They can be demonstrated in the LE and ME views. Spontaneous contrast is often seen in the Fontan circuit and represents slow flow along this venous pathway. TEE is particularly helpful in identifying thrombus formation along the Fontan pathway and during cardiac catheterization procedures aimed at creating, enlarging, or occluding a fenestration [192]. Adult patients who have undergone prior Fontan procedures may need revision of the intervention for either thrombotic complications or other problems. The Fontan conversion procedure aims for a more favorable hemodynamic modification.

Summary

Over the years, the use of TEE has become a valuable adjunct to interventional procedures, surgical, hemodynamic, and anesthetic management in the patient with CHD. In the cardiac catheterization laboratory, TEE provides procedural guidance, assesses the success of the intervention, identifies complications, and enhances the overall safety of the procedure. In the intraoperative setting, TEE confirms the diagnosis, facilitates planning or refinements of the intervention, and immediately evaluates the operative results. TEE can detect suboptimal surgical results or complications, thereby likely avoiding the need for subsequent reoperations and reducing overall morbidity, mortality rates, and costs. Contributions to anesthetic care include real-time monitoring of ventricular filling and cardiac function, ensuring adequate cardiac de-airing, and allowing optimization of hemodynamic management strategies.

The overview presented regarding the contributions of TEE in patients with CHD demonstrates the impact of this technology on clinical care and its likely positive influence on outcomes. In most centers, the TEE imaging approach is considered the standard for intraoperative assessment.
during cardiac surgery and for many interventions in the cardiac catheterization laboratory. As the TEE technology continues to evolve, additional applications and contributions will probably be recognized for both children and adults with CHD.

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http://www.wiley.com/go/andropoulos/congenitalheart


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CHAPTER 13
Coagulation, Cardiopulmonary Bypass, and Bleeding

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Introduction

Managing the coagulation system during and after cardiopulmonary bypass (CPB) is an integral part of pediatric cardiac anesthesia and surgery. This management has become more focused and deliberate as our understanding of coagulation has grown, as surgical procedures on neonates and infants with complex heart defects have become the norm, and as pharmacologic and technological options have expanded. This chapter will begin by reviewing the coagulation pathway, its maturation, and alterations in that pathway caused by the pathophysiology of congenital heart defects. Issues involved with managing the coagulation system during CPB and modalities for controlling bleeding after CPB will also be discussed. Finally, techniques for blood conservation in the peri-CPB period will be examined.

Coagulation

Models of the coagulation pathway

The normal hemostatic mechanism that is triggered after vascular injury involves complex and concurrent interactions among platelets, coagulation proteins, and fibrinolytic mechanisms. The processes have been described as primary, secondary, and tertiary phases of hemostasis.

Primary hemostasis reduces bleeding in damaged vessels by inducing vasoconstriction at the site of vessel injury and by initiating platelet adhesion, activation, and aggregation to form a platelet plug. Platelets adhere to exposed subendothelial tissues via an interaction between von Willebrand factor (vWF) and the glycoprotein (Gp) Ib receptor on platelet surfaces. Subsequently, upon activation, platelets release numerous hemostatic mediators from their granules, change the charge on their surface membranes to form an active surface on which the coagulation proteins interact, and express Gp IIb/IIIa fibrinogen receptors on their surfaces. Fibrinogen then binds to these exposed receptors, causing platelets to aggregate to each other [1] (Figure 13.1).

Secondary hemostasis leads to the formation of a fibrin clot by sequentially activating circulating coagulation factors to finally form insoluble fibrin. Our understanding of this secondary hemostasis has evolved from the traditional description of independent “intrinsic” and “extrinsic” coagulation pathways being activated in plasma to a “cell-based” concept of coagulation factors interacting on the surfaces of tissue factor (TF)-bearing cells and activated platelets at the site of vascular injury [2] (Figure 13.2). Secondary hemostasis begins with the activation of factor VII upon its exposure to TF, a transmembrane glycoprotein found on the cells of the subendothelial tissue of damaged blood vessels. The activated factor VII (VIIa) and TF form
Chapter 13 Coagulation, Cardiopulmonary Bypass, and Bleeding

Platelet
GpIb
Fibrinogen
GpIIb/IIIa
Adhesion
Activation:
- Change of shape
- Degranulation

Figure 13.1 Primary hemostasis. Platelet adhesion is mediated via von Willebrand factor (vWF) and platelet receptor glycoprotein Ib (GpIb). Subsequent aggregation is mediated via GpIIb/IIIa receptors. (Source: Hardy [1]. Reproduced with permission.)

Figure 13.2 Tissue factor-initiated, cell based hemostasis. TF, tissue factor; vWF, von Willebrand factor; TFPI, tissue factor pathway inhibitor. (Source: Monroe et al. [2]. Reproduced with permission of Thieme.)

a complex on these subendothelial cells. The cell-bound VIIa/TF complex then activates factor X (to Xa) and factor IX (to IXa). This sequence of activations was formerly called the “extrinsic pathway” of coagulation because a factor “extrinsic” to the blood, i.e. TF, is required for it to proceed. The newly formed factor Xa complexes with factor Va on the surface of TF-bearing cells and generates small amounts of thrombin (IIa) from prothrombin (II). This initially formed small amount of thrombin, while insufficient to initiate fibrin formation, activates platelets and factors V, VIII, and XI [3]. These activated platelets not only participate in the primary hemostasis process but also provide the active surface upon which further coagulation processes occur that result in fibrin formation.

At the same time, the contact of blood with the negatively charged subendothelial tissue of damaged blood vessels activates the contact factors (factors XI and XII, prekallikrein [PK], and high–molecular-weight kininogen [HMWK]). The result of this activation plays roles not only in the coagulation system but also in the related inflammatory response. From the coagulation perspective, this activation provides another route of activation of factor XI in addition to that formed by the actions of the cell-bound VIIa/TF complex. This coagulation sequence was formerly called the “intrinsic pathway” because all the contact factors are “intrinsic” to the blood.

At this point, activated coagulation factors and activated platelets work together to finally produce fibrin. Factor IXa formed by the actions of both the TF/VIIa complex and factor Xla joins with factor VIIIa on the surface of activated platelets to activate substantial amounts of factor Xa. This factor Xa then joins with factor Va, again on the platelet surfaces, to form the prothrombinase complex, which subsequently generates large bursts of thrombin. This thrombin then converts fibrinogen into the fibrin strands necessary for clot formation [3].

Tertiary hemostasis involves fibrin clot maturation and fibrinolysis. Factor XIII is activated to cross-link the fibrin strands. This cross-linked fibrin restores hemostasis in an injured blood vessel by acting as the “mortar” that cements the primary platelet plug. Eventually, after the injured blood vessel has healed, thrombus is removed by fibrinolysis in order to re-establish normal blood flow through the repaired vessel. Circulating plasminogen binds to fibrin within the thrombus. Tissue plasminogen activator (tPA) released from endothelial cells also complexes with fibrin and converts the bound plasminogen to its active form plasmin, leading to the enzymatic degradation of the clot. Further formation of plasmin also occurs as a result of the direct actions of factor XIIa and kallikrein from the contact activation system on plasminogen [4].

The formation and dissolution of a thrombus by these mechanisms are closely regulated by many feedback inhibitors to keep the coagulation process localized to the area of blood vessel injury. Thrombin is directly inhibited by antithrombin III (ATIII), heparin cofactor II (HCII), and \( \alpha_2 \)-macroglobulin (\( \alpha_2 \)M). ATIII plays the major role in this inhibition although the role of \( \alpha_2 \)M assumes more significance in infants because of its elevated level in this population [5]. Thrombin is indirectly inhibited by protein C (PC), protein S (PS), and tissue factor pathway inhibitor (TFPI). Free plasma thrombin binds to an endothelial cell receptor, thrombomodulin, and this complex activates PC. Activated PC in the presence of PS inactivates factors Va and VIIIa, thus inhibiting the formation of more thrombin. TFPI forms a complex with factor Xa that inhibits factor VIIa and thus the generation of thrombin as well [5,6] (Figure 13.3).

The fibrinolytic system is also balanced by inhibitors in order to control the extent of fibrinolysis. The activity of any circulating tPA is inhibited by plasminogen activator inhibitor (PAI) type 1. Ongoing formation of plasmin is prevented when thrombin-activatable fibrinolysis inhibitor (TAFI) cleaves the lysine residues from
degrading fibrin to which tPA and plasminogen must bind in order to interact and form plasmin. Finally, circulating plasmin itself is inhibited by alpha-2 antiplasmin [7]. Interactions between coagulation activators and inhibitors contain the coagulation process to the site of blood vessel injury and provide a balance between bleeding and thrombosis.

**KEY POINTS: MODELS OF THE COAGULATION PATHWAY**

- Primary hemostasis involves vasoconstriction of injured vessels and platelet plug formation.
- Secondary hemostasis involves coagulation factor activation, resulting in fibrin clot formation, and is better described using a cell-based concept.
- Tertiary hemostasis involves cross-linking of fibrin strands and, eventually, fibrinolysis.

**Maturational factors**

In considering the coagulation processes in children, it is important to note that at birth the coagulation system is immature and continues in a state of maturation throughout at least the first year of life. While maternal coagulation factors do not cross the placenta, the components of the coagulation system begin to appear in the fetus after approximately 10–11 weeks of gestation. The levels of coagulation factors at birth depend on the gestational age of the newborn, with major increases occurring between 30 and 40 weeks of gestation. This maturational process affects plasma levels of both procoagulants and coagulation inhibitors [8] (Table 13.1). By 6 months of age, most of these factor levels have equilibrated between premature and full-term infants and most have reached adult ranges as well, although mean levels are still lower than adult levels [5,6,9]. In addition to these quantitative deficiencies, functional immaturity is also seen in several coagulation factors. The combination of these quantitative and qualitative deficiencies affects all three phases of hemostasis.

In the primary hemostatic process, platelet counts at birth are similar to those found in older children and adults [10]. However, vWF levels are elevated at birth compared with levels measured in adults [11,12], as is the percentage of larger vWF multimers, the vWF molecules most important in effecting adherence between platelets and injured blood vessel walls [13]. In vitro platelet function studies have found platelet adhesiveness in neonates to be similar to that in adults, but have found platelet aggregation in response to various agonists as well as platelet granule secretion to be impaired [9,14,15]. Although results of functional tests of platelet activity seem at odds in neonates and young infants (bleeding times are prolonged [16] whereas platelet function analyzer closure times are shorter [17]), primary hemostasis appears to remain intact in neonates and children.

Many of the coagulation factors involved in secondary hemostasis are quantitatively deficient in neonates. At birth, mean levels of the vitamin K-dependent procoagulant factors (thrombin, VII, IX, and X) and the contact factors (XI, XII, PK, and HMWK) are less than 70% of adult levels and still lag behind adult levels even at 6 months of age. Only fibrinogen and factors V and VIII exist at levels in neonates similar to those found in adults [10–12]. However, fibrinogen has been postulated to exist in a dysfunctional “fetal” form in the neonate, based on observations of prolonged thrombin and reptilase times, tests that measure the rate of conversion of fibrinogen to fibrin after the addition of an exogenous stimulator (thrombin or reptilase) [18,19], and based on differences

<table>
<thead>
<tr>
<th>Component</th>
<th>Neonatal vs. adult level</th>
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<tbody>
<tr>
<td>Primary hemostasis</td>
<td>← Platelet count</td>
</tr>
<tr>
<td>vWF</td>
<td>↑</td>
</tr>
<tr>
<td>Coagulation factors</td>
<td>↓ FII, FVII, FIX, FX</td>
</tr>
<tr>
<td>↓ FXI, FXII</td>
<td></td>
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<tr>
<td>↓ to ← FV, FXIII</td>
<td></td>
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<tr>
<td>← Fibrinogen</td>
<td></td>
</tr>
<tr>
<td>↑ FVIII, vWF</td>
<td></td>
</tr>
<tr>
<td>Anticoagulant factors</td>
<td>↓ TFPI, AT, PC, PS</td>
</tr>
<tr>
<td>↑ α2M</td>
<td></td>
</tr>
<tr>
<td>Fibrinolysis</td>
<td>↓ Plasminogen</td>
</tr>
<tr>
<td>← to ↑ PAI</td>
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</table>

vWF, von Willebrand Factor; F, factor; TFPI, tissue factor pathway inhibitor; AT, antithrombin; PC, protein C; PS, protein S; α2M, α₂-macroglobulin; PAI, plasminogen activator inhibitor. Source: Guzzetta and Miller [8]. Reproduced with permission of Wiley.
between immunologic and functional assays of fibrinogen in fetal blood [20]. Additionally, not until children are older than 12 months of age do their fibrinogen levels correlate with thromboelastogram parameters known to correlate with fibrinogen levels in adults [21]. Mean levels of most of the coagulation inhibitors, including ATIII, HCII, PC, PS, and TFPI, also lag behind adult levels during most of infancy. Only α,M levels in newborns are equivalent to those found in adults and these levels actually rise during infancy to exceed adult levels [11,12,20].

In the presence of these quantitative and qualitative deficiencies in factors involved in secondary hemostasis, studies have shown that the ability of the plasma of young children to generate thrombin is significantly less than that of adults [22]. Nevertheless, mean values of the prothrombin time (PT), which is touted to assess the “extrinsic” coagulation system, are similar in neonates and infants to those found in adults, although a greater variability in values is seen [11,12]. Variations in the balance between vitamin K-dependent procoagulants (thrombin, VII, IX, and X) and vitamin K-dependent coagulation inhibitors (PC and PS), all of which are quantitatively deficient in young children, may account for this variability. The activated partial thromboplastin time (aPTT), used to assess “intrinsic” coagulation, is prolonged in neonates before falling to adult values by 3–6 months of age. Quantitative deficiencies in the contact activation factors (XI and XII) probably account for this finding [11,12].

Tertiary hemostasis mainly involves the fibrinolytic removal of thrombus via the activity of plasmin to re-establish blood flow through repaired vessels. In newborns, plasminogen levels are only 25–60% of those found in adults and remain at low levels until after 6 months of age [5,23]. Additionally, plasminogen may also exist in a qualitatively dysfunctional form in newborns [24]. Levels and activity of plasminogen’s major in vivo activator, tPA, are similarly low in newborns. Meanwhile, activity of the major inhibitor of plasminogen activation, PAI, is similar in newborns and adults. As a result of these imbalances, not only is plasmin generated at much slower rates in newborns but also five times the amount of tPA is required in newborns to achieve the level of plasmin generation found in adults [23].

In spite of these maturational deficiencies, the infrequency of spontaneous hemorrhage or thrombosis in neonates and infants suggests a relative balance between procoagulants and their inhibitors. If anything, the process tends towards increased coagulability. Thrombotic complications are more common in neonates and thromboelastography (TEG) has shown that neonates and infants actually clot faster and have increased clot strength compared with adults [25]. Even with the maintenance of functional integrity in the coagulation system of infants, the effect of the maturational deficiencies in their coagulation systems is that these children have little margin of safety once they encounter the further alterations in hemostasis produced by exposure to CPB.

### In vivo

**Influence of congenital cardiac pathophysiology**

Aside from the maturational effects on coagulation factor levels and function, the presence of congenital heart defects seems to impose further alterations on baseline coagulation profiles. Coagulation abnormalities have been reported in 58% of children with non-cyanotic defects [26]. Prolonged bleeding times, decreased fibrinogen levels, and baseline fibrinolytic activity were noted, especially in infants. Children with cyanotic defects have been shown to have a 71% incidence of coagulation abnormalities [26], including defective platelet adhesion and aggregation, decreased levels of fibrinogen and the vitamin K-dependent factors (II, VII, IX and X), and accelerated fibrinolysis [27–30]. Children with cyanotic defects whose hematocrits exceed 50% have significantly worse baseline coagulation deficiencies than those whose hematocrits are less than 50%, and cyanotic children older than 3 years of age have worse abnormalities than younger cyanotic children [31]. The severity of the polycythemia correlates with the number of hemostatic abnormalities present preoperatively [27]. Children with either cyanotic or acyanotic heart defects who have preoperative coagulation abnormalities have been found to be more likely to experience excessive bleeding associated with their cardiac surgeries [26,27]. However, months after corrective surgery, improvement or complete correction of pre-existing baseline coagulation abnormalities has been found [26]. This probably relates to amelioration by the surgery of the proposed major etiology of these abnormalities: hepatic dysfunction from hypoperfusion or from perfusion with hypoxic, hyperviscous blood [28].

Most of these data are from studies conducted several decades ago. In the current world of pediatric cardiac surgery where corrective procedures are performed early in the lives of affected children, many of these congenital heart defect-induced coagulation abnormalities may be less common. However, those children with single-ventricle anatomy and physiology who live with a degree of arterial desaturation do continue to develop cardiac pathophysiology-induced coagulation abnormalities. In these children, significantly decreased levels of fibrinogen, the vitamin K-dependent factors (II, VII, IX,
and X), and factors V and VIII, as well as the coagulation inhibitors ATIII, PC, and PS and plasminogen have been demonstrated after initial palliative procedures but before a Glenn anastomosis is performed [32]. Virtually all of these abnormalities of procoagulants, coagulation inhibitors, and plasminogen continue to be apparent a couple of years later immediately prior to a Fontan procedure as well [33]. While no specific hemodynamic variables are predictive of the occurrence of these deficiencies at either of these time points, ventricular dysfunction prior to a Glenn anastomosis and longer intervals between the Glenn anastomosis and the Fontan procedure do correlate with the significance of these abnormalities [32,33]. Even after completion of a Fontan procedure, abnormalities of both procoagulants and coagulation inhibitors persist in an imperfect balance that undoubtedly contributes to the significant incidence of thromboembolic events that occur in these patients [34].

**KEY POINTS: INFLUENCE OF CONGENITAL CARDIAC PATHOPHYSIOLOGY ON COAGULATION**

- Baseline coagulation defects exist in many children with congenital heart defects, probably because of hepatic hypoperfusion or hypoxia.
- Children with hematocrit > 50% are more significantly affected.
- Coagulation abnormalities persist in children with single-ventricle anatomy and physiology through and after all stages of palliation.

**CPB-associated coagulation changes**

**Anticoagulation**

Anticoagulation is a coagulation change mandated, rather than produced, by CPB. Because of its instant action and ease of neutralization, heparin is used to achieve this anticoagulation. Although heparin by itself has little anticoagulant activity, it acts by binding to ATIII and, consequently, greatly accelerating the inhibition of thrombin and other activated coagulation factors by ATIII. Heparin also inhibits the factor Xa-catalyzed formation of thrombin via an ATIII-independent mechanism [35].

The adequacy of heparin-induced anticoagulation can be measured clinically either by assessing heparin’s effect with the activated clotting time (ACT) or by measuring its whole-blood or plasma level. None of these measurements is ideal, though. ACT values are influenced by factors that do not contribute to anticoagulation, such as hypothermia and hemodilution [36], both of which are commonly encountered in young children during CPB. Indeed, when neonates and infants are given a standard weight-based heparin dose, their ACTs are prolonged to values deemed acceptable for the conduct of CPB, yet evidence of thrombin generation is still apparent [37–39]. Additionally, one would reasonably anticipate that the effect of heparin as assessed by the ACT would depend on plasma levels of ATIII, heparin’s major cofactor, if the prolongation of the ACT after heparin administration was completely due to a true anticoagulant effect. In adults and older children, the increase in ACT values in response to heparin administration is indeed proportional to plasma ATIII levels [38]. In neonates and infants, though, there is no correlation between plasma ATIII levels and the ACT response to heparin administration [38,39]. Levels of heparin cofactor II and α2M, two other heparin cofactors, also do not correlate with ACT values in these patients after heparin administration [39]. Additionally, even when considering the multiple methods available for measuring the ACT, most ACT measurements do not correlate with heparin levels in neonates and children during the course of CPB [40,41]. Thus, the adequacy of the ACT in confirming acceptable anticoagulation in the youngest of children is questionable.

Heparin levels can be measured in whole blood at the bedside using protamine titration or in plasma in a central hospital laboratory using a chromogenic assay. Whole-blood bedside measurements are much more convenient and timely for clinical practice and have been found to correlate with the “gold standard” laboratory plasma measurements in young infants [41]. Plasma measurements, however, are consistently higher than the whole-blood measurements. A drawback to relying on measurements of heparin levels is that they do not take into account the tremendous variability in individual patient responses to heparin.

Ultimately, the adequacy of heparin-induced anticoagulation is reflected by the level of inhibition of both thrombin generation and thrombin activity during CPB. Less thrombin is generated, less fibrinogen consumed, and less fibrinolysis initiated when children are managed by individualized protocols based on the maintenance of a specified whole-blood heparin level as compared with standard heparin dosing protocols based on patient weight and monitored by ACT measurements [42–44]. While ACT values remain acceptably prolonged by both protocols, heparin levels begin to diverge between the two protocols within 60 minutes of the initiation of CPB, falling significantly in the children dosed with the weight-based protocol [43]. The use of a heparin concentration-based protocol results in the administration of significantly more heparin when compared with a weight-based protocol. While more protamine may be necessary to neutralize this additional heparin [44], 24-hour postoperative chest tube drainage has not been found to differ between the protocols [42–44]. In fact, lower postoperative transfusion requirements have been shown using a heparin concentration-based protocol [42,44], although the target heparin concentration may need to be lowered in infants to maintain this advantage [44]. Improvement in clinical outcomes as reflected by shorter durations of postoperative mechanical ventilation and shorter intensive
In practice, many more institutions manage intraoperative heparin administration by monitoring ACT values rather than heparin level measurements. An ACT is certainly easier and less expensive to obtain. When using only ACT measurements, anesthesiologists and perfusionists should keep in mind that heparin levels in children fall significantly within 1 hour of CPB despite the maintenance of adequate ACT values and should consider the administration of additional heparin if CPB is expected to continue for a substantial period of time.

**KEY POINTS: ANTICOAGULATION**

- The adequacy of heparin-induced anticoagulation for CPB can be assessed by tests of heparin’s effect (ACT) or by measuring its blood levels.
- ACT values are affected by factors other than heparin-induced anticoagulation.
- An individualized heparin level-based protocol probably results in better thrombin inhibition.

**Heparin-induced thrombocytopenia**

A potential problem associated with the use of heparin is heparin-induced thrombocytopenia (HIT). This immune-mediated syndrome (formerly termed “type II” HIT) can cause limb- and life-threatening vascular thromboses (38–76% incidence), carries a mortality rate of 20–30% [45], and has been reported in adults, children, and even neonates. The pathogenesis involves heparin-induced generation of immunoglobulin G (IgG) that binds multimolecular complexes of heparin and platelet factor 4 (PF4) on platelet surfaces leading to a self-perpetuating cycle of platelet activation, thrombin formation, and further release of PF4 from platelet granules. Endothelial cells and monocytes are also activated by the antiheparin/PF4 IgG, resulting in expression of intravascular TF and further procoagulant activity [45,46].

The diagnosis of HIT requires the presence of both clinical and laboratory criteria. Clinical criteria include thrombocytopenia (decrease in platelet count to < 150,000/mm³ or to ≤ 50% of baseline) with or without venous or arterial thromboses. Laboratory criteria include positive antigen assays (detect antibodies to heparin–PF4 complexes) and positive functional tests of platelet activation or aggregation [45–47].

In children, HIT has been reported to occur in 2.3–3.7% of those receiving heparin, with a bimodal distribution showing peaks during the neonatal/infant period and during puberty [48,49]. The use of intravascular catheters and associated heparin flushes in neonates and the hormonal changes, incidence of smoking, and the use of contraceptive medications at puberty may help explain the timing of these peaks [50]. However, others have doubted the occurrence of HIT in neonates and found a very low incidence in children. They proposed that immaturity of an immunologic response in neonates as well as low circulating levels of PF4 and diminished ability of heparin to bind proteins in young children may explain these low incidences [46,51,52]. Unfractionated heparin (UFH) derived from bovine lung is more likely to induce HIT than that derived from porcine intestinal mucosa. Both types of UFH are more likely to induce HIT than is low-molecular-weight heparin (LMWH), probably because the shorter chain length of LMWH causes weaker binding to PF4 and thus less IgG production [46,53].

Heparin-induced thrombocytopenia can present as one of three scenarios. “Typical onset” HIT is seen in about two-thirds of cases and presents as a falling platelet count beginning 5–10 days after starting heparin administration. “Rapid onset” HIT comprises about 30% of cases and occurs abruptly in the first hours or days of heparin administration in patients who presumably have persistent heparin–PF4 antibodies due to heparin exposure within the previous 100 days. “Delayed onset” HIT is rare but presents up to 3 weeks after discontinuation of heparin, presumably because persistent antibodies can activate platelets even in the absence of heparin [46,48,54].

The work-up of thrombocytopenia and/or new thrombosis after heparin exposure in patients of any age begins by assessing the probability of HIT using the “four Ts”: thrombocytopenia; timing of platelet count fall; thrombosis; and other causes for thrombocytopenia [46] (Table 13.2). Other potential causes of thrombocytopenia (“pseudo-HIT” disorders) include sepsis, pulmonary embolism, diabetic ketoacidosis, adverse effect of a drug other than heparin, antiphospholipid antibody syndrome, post-transfusion purpura, and non-immune heparin-associated thrombocytopenia (HAT, formerly termed “type I” HIT) [54]. HIT is very unlikely in a patient with a low probability score and thus no laboratory tests or change in therapy are necessary. Patients with a high probability score need only a positive antigen assay to confirm the diagnosis. Patients with intermediate scores will need positive antigen and functional assays to make the diagnosis of HIT [55].

Antigen assays detect the presence not only of IgG antibodies to heparin–PF4 complexes but also of IgA and IgM antibodies that also form to these complexes [48]. However, it is controversial as to whether IgA and IgM antibodies can mediate HIT in the absence of IgG antibodies [46,54]. This explains why up to 50% of heparin-treated adult patients develop detectable heparin–PF4 antibodies, yet only 1–5% develop HIT [45], why antigen tests are so sensitive in helping to diagnose HIT, and why positive antigen tests alone do not definitively diagnose HIT [56]. Antigen assays usually have a short turnaround time and can be performed in many peripheral laboratories [49].
### Table 13.2 Estimating the Pretest Probability of Heparin-Induced Thrombocytopenia: the “four Ts”

<table>
<thead>
<tr>
<th>Points (0, 1, or 2 for each of four categories: maximum possible score = 8)</th>
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<tbody>
<tr>
<td>2</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>Timing* of platelet count fall or other sequelae</td>
</tr>
<tr>
<td>Thrombosis or other sequelae (e.g. skin lesions)</td>
</tr>
<tr>
<td>Other cause for thrombocytopenia not evident</td>
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Pretest probability score: 6–8, high; 4–5, intermediate; 0–3, low.

*First day of immunizing heparin exposure is considered as day 0; the day the platelet count begins to fall is considered the day of onset of thrombocytopenia (it generally takes 1–3 days more until an arbitrary threshold that defines thrombocytopenia is passed).


Functional tests detect the ability of the heparin–PF4–IgG complex to activate platelets and thus to cause the thrombosis so commonly seen in HIT. Therefore, the specificity of these tests is increased. The serotonin release assay is considered the “gold standard” in HIT functional assays because of its combined high specificity and sensitivity. Functional assays are time-consuming, require donor platelets, and are performed only in reference laboratories [48,49].

Treatment for clinically suspect HIT should begin before confirmatory laboratory test results are received, because of the significant risk of the development or propagation of thrombosis. Discontinuation of all sources of heparin exposure is of paramount importance. This includes not only UFH being given intravenously, subcutaneously, or in flushes, but also heparin-coated catheters and LMWH. Concurrently, an alternative non-heparin anticoagulant should be started. Alternative antithrombin-dependent anticoagulants include danaparoid and fondaparinux. These drugs are direct factor Xa inhibitors. Danaparoid is not FDA-approved and was withdrawn from the US market in 2002. Fondaparinux is a synthetic pentasaccharide that has a long half-life, is given as a once-daily subcutaneous dose, and has no antidote. Its use has mainly been in postoperative orthopedic adult patients.

The direct thrombin inhibitors, lepirudin, bivalirudin, and argatroban, are most commonly used. These drugs form complexes with thrombin and prevent it from converting fibrinogen to fibrin and from activating platelets. Each has been approved for use in some HIT scenario in adults, although none of them is approved for use in children. They have no reversal agents and are monitored using the aPTT, ACT, or ecarin clotting time. They all prolong the international normalized ratio (INR), especially argatroban, thus complicating an eventual transition to warfarin. They are excreted by various mechanisms (lepirudin, renal; bivalirudin, renal and enzymatic; argatroban, hepatic). Lepirudin binds irreversibly to thrombin, thus giving it a longer half-life than the other two with their reversible thrombin binding. None of these drugs cross-reacts with heparin–PF4 antibodies. However, lepirudin administration frequently leads to antihirudin antibody development, as lepirudin is derived from leech salivary glands and is thus a foreign protein to the human body. As anaphylaxis can occur on re-exposure, lepirudin should probably be used only once in a patient’s lifetime. Dosing schedules for children have been derived from those of adults but have varied tremendously in the literature [46,48,49,53,54].

Several paradoxes in the treatment of HIT are noteworthy. Despite its lower frequency of causing HIT, LMWH is contraindicated because of its high cross-reactivity with UFH-induced heparin–PF4 antibodies. Prophylactic platelet transfusions for thrombocytopenia are relatively contraindicated as they may increase the thrombotic risk of HIT and because bleeding is rarely a problem in HIT. Coumarins (warfarin) should be avoided in acute HIT because their initial inhibition of protein C may accelerate the thrombotic process. Warfarin should only be administered after the platelet count has recovered (>150 × 10⁹/L) and its institution should overlap the ongoing administration of a direct thrombin inhibitor. Warfarin should be continued for at least 1 month in patients with HIT and no associated thrombosis (“isolated HIT”) and for a minimum of 3–6 months for patients with HIT-associated thrombosis (“HIT thrombosis syndrome”) [46,53,54].
When a patient with a history of HIT requires elective cardiac surgery, every effort should be made to postpone the surgery until the heparin–PF4 antibody levels have become negative (median of 85 days). At that time, it will be safe to administer heparin for CPB, although some advise against the repeat use of heparin in patients with a previously proven episode of HIT. Fortunately, there is little immune memory in HIT, so antibodies are usually not re-stimulated upon re-exposure to heparin and, even if they are, they are usually not regenerated before 5 days after the re-exposure [46]. Even so, heparin should not be used during preoperative cardiac catheterization or in flushes for transducer systems or intravenous or intra-arterial catheters. Additionally, heparin-coated catheters and extracorporeal circuit components should be avoided. If postoperative antithrombosis prophylaxis is needed in these patients, a non-heparin anticoagulant should be used [56]. If a patient with a history of HIT requires cardiac surgery while heparin–PF4 antibodies are still present, anticoagulation for CPB must be accomplished either by using one of the non-heparin anticoagulants or by administering an antiplatelet agent such as epoprostenol (prostacyclin analog) or tirofiban (GpIIb/IIIa inhibitor) in conjunction with heparin [46].

**KEY POINTS: HEPARIN-INDUCED THROMBOCYTOPENIA (HIT)**

- HIT results from heparin-induced formation of antibodies against heparin–PF4 complexes on platelet surfaces.
- The diagnosis of HIT requires both clinical (thrombocytopenia, thrombosis) and laboratory (antigen assays or functional tests) criteria.
- Treatment of HIT involves discontinuing all sources of heparin exposure and administering a non-heparin anticoagulant.

**Exposure to the CPB circuit**

A couple of things about a CPB circuit are obvious. One is that its internal surface is non-physiologic compared with the endothelial lining of blood vessels. When a patient’s blood is exposed to this surface, activation of the coagulation, fibrinolytic, and inflammatory systems is initiated. Another is that a certain amount of some type of fluid must be used to fill the circuit prior to the commencement of CPB. Thus, some degree of hemodilution results. Both of these issues contribute to the deleterious consequences of the use of CPB during surgeries for CHDs.

Activation of factor XII leads to initiation of the coagulation system through activation of factor XI and to initiation of the fibrinolytic and inflammatory systems through conversion of PK to kallikrein [4] (Figure 13.4).

The generation of thrombin during CPB is well documented [37,57], despite administration of adequate amounts of heparin to prevent catastrophic cloting. Contact of the patient’s blood with the non-physiologic surfaces of the CPB circuit activates the contact factors (XI, XII, PK, and HMWK) [4]. Contact factor-induced activation of the coagulation system plays a role, as does exposure of TF on membranes of cells traumatized by aspiration from the surgical field, expression of TF on monocytes involved in the inflammatory process [58], and thrombin-induced release of TF and vWF from endothelial cells [59].

Activation of the fibrinolytic system during CPB in children is also well documented [60–62]. The fibrinolytic system is stimulated as plasminogen is converted to plasmin by tPA released from endothelial cells through the actions of kallikrein formed from contact activation of PK, of thrombin, and of surgical trauma [63,64]. Although fibrinolytic activity seems to resolve after the conclusion of CPB [60,62], activation of both coagulation and fibrinolysis combine to damage platelets during CPB. After CPB, platelet adhesion is decreased due to destruction of GpIb receptors by plasmin and by the shear stresses encountered during CPB [65]. Additionally, platelet aggregation is diminished because platelet activation during CPB by thrombin, plasmin, and fibrin split products depletes platelets of their granules and interferes with their subsequent ability to aggregate to each other [66] (Figure 13.5). The cumulative result of these processes is the quantitative or qualitative consumption of coagulation factors and platelets during CPB that plays a significant role in post-CPB bleeding in children [67].

The inflammatory system is also activated after exposure to the CPB circuit via contact activation with its generation of factor XIIa, thrombin, kallikrein, and products of fibrinolysis as well as by heparin–protamine complexes and by circulating endotoxin that is released from CPB circuit components, intravenous fluids, blood products, or the intestinal tract [68]. This results in the activation of...
complement proteins, neutrophils, and endothelial cells and the generation of inflammatory cytokines that lead to increased vascular permeability, neutrophil infiltration into tissues, and production of “acute phase proteins” (Figure 13.6). The resulting tissue damage and organ dysfunction leads to “postperfusion syndrome,” which compromises cardiac, pulmonary, and renal function and promulgates the coagulopathy that follows exposure to CPB.

Another problem encountered upon the initiation of CPB is hemodilution. This dilution is most significant in the youngest patients because of the baseline maturational deficiencies in many coagulation factor levels. The current practice of performing open-heart surgery in neonates and young infants, as well as the accumulating evidence about potentially deleterious effects of transfused blood products, has prompted efforts to decrease CPB circuit volumes [69]. In the past, priming volumes of the circuits were two to four times the blood volume of neonates and infants, thus producing profound post-CPB alterations in coagulation factor levels due to hemodilution [70–72]. These large circuits also amplified the degree of contact activation with the corresponding activation of coagulation, fibrinolytic, and inflammatory systems, because of the larger non-physiologic surface areas they presented [73]. Contemporary circuits have been miniaturized by reducing arterial and venous tubing diameters and lengths, by reducing priming volumes of oxygenators, cardioplegia sets, and suction and vent tubings, and by shortening pump raceways. Other efforts include the elimination of arterial line filters and the use of vacuum-assisted venous drainage, but these maneuvers carry some risks and have not been universally adopted [69,73]. As a result of these modifications, circuits are now available whose priming volume may be as little as 140–172 mL for small infants (~5 kg) [73,74]. Use of these circuits has resulted in an attenuated inflammatory response to CPB and in significant reductions in the transfusion of banked blood that will hopefully translate into improved clinical outcomes [69,73,74].

KEY POINTS: CPB CIRCUIT-INDUCED COAGULATION ALTERATIONS

- Activation of contact factors and hemodilution occur at the commencement of CPB.
- Contact factor activation leads to activation of coagulation, fibrinolytic, and inflammatory processes that may result in “postperfusion syndrome.”
- Both contact activation and hemodilution have been attenuated by miniaturization of contemporary CPB circuits, resulting in an attenuated inflammatory response and reduced transfusion requirements.

Figure 13.5 Proposed mechanism for the development of platelet dysfunction during cardiopulmonary bypass. HMWK, high-molecular-weight kininogen; K, kallikrein; PK, prekallikrein. (Source: Carr et al. [66]. Reproduced with permission of CME Network.)

Figure 13.6 Mechanisms and subsequent effects of complement activation. (Source: Miller & Levy [68]. Reproduced with permission of Elsevier.)
Management of bleeding after CPB

Predictors of post-CPB bleeding

Knowing which children are likely to bleed excessively after CPB would certainly be helpful preoperatively. Not only could the blood bank staff then have the appropriate blood and blood products available, but the operating room staff could also have the appropriate expectations of the day! Many demographic, laboratory, and surgical variables have been studied in attempts to identify specific factors that can consistently make this prediction. Patient age and weight appear to be the demographic variables with the most significant associations. Greater blood loss should be anticipated in children less than 12 months of age [75], with neonates being at greatest risk [76], and/or in infants weighing less than 8 kg [71]. The preoperative presence of cyanosis is also associated with increased post-CPB blood loss and transfusion requirements [77].

Batteries of preoperative laboratory tests have been examined to determine their abilities to predict excessive post-CPB bleeding. Few associations have been found, and those associations are weak at best [78]. Even when correlations are identified, they can often be seen only in retrospect, as the value of the preoperative test in any given child who turns out to bleed excessively may have been at the limits of normal and thus may not have stood out preoperatively as an abnormal result. This inability of preoperative laboratory tests to consistently segregate children who bleed excessively probably relates to the previously discussed coagulation changes that occur during CPB as a result of activation of the coagulation and fibrinolytic cascades and hemodilution. Thus, preoperative test values and values after CPB, which may actually be helpful in distinguishing excessive bleeders, are significantly different. Nevertheless, a high preoperative hematocrit level (surrogate for cyanotic heart disease), prolonged aPTT, and certain TEG parameters (reduced K and maximum amplitude values) were associated with 12-hour chest tube drainage in one study of 482 children [79].

Several surgical variables definitely correlate with the amount of post-CPB bleeding and blood product transfusion. Not unexpectedly, repeat sternotomy, the complexity of procedures as indicated by the duration of CPB and the degree of hypothermia during CPB, and the cumulative inotropic support are all significant predictors. The surgeon and anesthesiologist involved in the procedure have also been found to be correlating factors [75,78,80].

Use of coagulation tests to manage post-CPB bleeding

Differentiating surgical from coagulopathic bleeding at the conclusion of CPB can be a difficult task that leads to interesting discussions between surgeons and anesthesiologists! Multiple coagulation tests have been examined in attempts to identify one that can be deemed the “gold standard” for determining the etiologies and the significance of coagulation derangements after CPB. As platelet abnormalities (in both number and function) and hypofibrinogenemia are the two most common causes of coagulopathic bleeding after CPB [79,81], it is not surprising that platelet counts, fibrinogen levels, and TEG K, a, and maximum amplitude values (all dependent on platelet–fibrinogen interactions) at the end of CPB have demonstrated independent correlations with postoperative chest tube drainage in children [71,82]. However, identification of a “gold standard” coagulation test has remained elusive.

In adult patients, the use of an algorithm based on either standard laboratory coagulation tests (PT/INR, aPTT, ACT, platelet count, fibrinogen level) or point-of-care tests (Hepcon analyzer, TEG, platelet function analysis) has been shown to decrease packed red blood cell (PRBC) and blood component transfusions after CPB compared with using only clinical judgment based on the appearance of the surgical field [83–85]. However, other than reducing unnecessary transfusions, evidence that the use of algorithms based on coagulation tests can otherwise improve outcomes in children after cardiac surgery is limited [81]. To date, no validated algorithm for use in children after CPB has been established [86]. Important work remains to be done to determine trigger points of available coagulation tests that would indicate the need for specific blood component transfusions.

Despite the lack of validated algorithms, coagulation tests can still provide guidance for dealing with “wet” operative fields. In order to do so, test results must be quickly available to clinicians. Technology currently exists to allow on-site measurements of whole-blood PT, aPTT, and platelet counts in the operating room [83]. Point-of-care tests of platelet function (Sonoclot analyzer, PFA-100, and MultiPlate platelet aggregometer) are also available [81]. Thromboelastograms can be activated with celite, kaolin, or tissue factor to provide rapid data as well [62,87]. Protamine or heparinase can be used to neutralize heparin in blood samples and thus to allow thromboelastograms to be obtained even during CPB while patients are anticoagulated [61,62]. With this modification, pertinent information can be available by the conclusion of CPB to guide blood component transfusions. After protamine administration at the conclusion of CPB, heparinase-modified TEGs can be helpful in discerning the contribution of residual circulating heparin, another identified cause of post-CPB bleeding [81], to persistently prolonged ACT values [88]. Finally, GpIIb/IIIa receptor antagonists such as abciximab can be used subsequently to tease out the relative contributions of platelets and fibrinogen to clot strength in order to more accurately direct therapy [21].

A few final points should be made about the use of coagulation tests to guide the management of post-CPB bleeding. The results of coagulation tests should never
replace the use of good clinical judgment. Even with evidence that the use of algorithms reduces transfusions, observation of the surgical field has proved accurate in identifying those patients who will subsequently bleed excessively [89]. Therefore, empirical intervention may be necessary in the face of active bleeding before coagulation test results are available. Once coagulation test results are available, remember that the clinical situation is dynamic, especially in the face of ongoing bleeding, and those results may no longer accurately reflect the clinical reality of the moment. Additionally, in the absence of clinical bleeding, therapy is not required even if some coagulation test results are abnormal [81]. Finally, not all coagulation defects, and thus tests, are of equal importance in their impact on post-CPB bleeding. Attention to and correction of those tests indicative of abnormalities with platelets and fibrinogen should command primary attention.

**Blood product transfusion**

Whole-blood or individual coagulation products can be used to manage post-CPB coagulopathies. Whole blood less than 48 hours old has been shown to better limit post-CPB blood loss in children less than 2 years of age undergoing complex surgical procedures when compared with the use of a reconstituted product composed of one unit each of PBCs, platelets, and fresh frozen plasma (FFP) [90]. This improvement in hemostasis was attributed to the presence of better functioning platelets in whole blood. Unfortunately, whole blood less than 48 hours old is not readily available in all pediatric cardiac surgical centers and, when it is, it has usually been stored at 4°C, which significantly depresses platelet function [91]. Additionally, the use of whole blood must be supplemented at times with the transfusion of individual coagulation products to optimally control post-CPB blood loss, especially in younger patients [70].

The transfusion of individual coagulation products is the primary treatment for post-CPB coagulopathies in children in many institutions. The effects of different coagulation products in correcting abnormalities of TEG parameters, platelet counts, and fibrinogen levels after prothrombin administration in children have been investigated [71]. As abundant evidence demonstrates that quantitative and qualitative platelet deficiencies [70,83,92,93] exist after CPB, initial treatment of ongoing bleeding after adequate heparin neutralization was with platelet transfusions. Platelet administration substantially improved the TEG parameters in addition to the platelet count. If bleeding continued, cryoprecipitate administration raised fibrinogen levels to normal and significantly further improved TEG parameters, whereas FFP not only failed to increase fibrinogen levels but also worsened all TEG parameters. Patients given platelets followed by FFP had substantially more 24-hour chest tube drainage and required more coagulation products postoperatively than those receiving cryoprecipitate. Therefore, when using component therapy to treat post-CPB coagulopathies in children, platelet transfusion followed by cryoprecipitate, if needed, seems the better approach to restore hemostasis [71].

Packed red blood cell transfusions occur more commonly in children during cardiac surgery than during any other operative procedure and account for more than half of all perioperative red blood cell (RBC) transfusions [94]. Although there is no doubt that RBC transfusions can be life-saving, several recent pediatric studies have demonstrated an increase in morbidity and mortality associated with RBC transfusions [95–97]. The optimal hemoglobin level for children undergoing cardiac surgery and CPB is unknown and probably varies depending on age, degree of cyanosis, and complexity of the operative procedure. Studies examining the use of restrictive vs. liberal RBC transfusion strategies suggest that a restrictive transfusion policy is safe, less expensive, and leads to shorter hospital stays [98,99]. It should be emphasized that the majority of these studies exclude neonates and children with cyanotic heart disease. One of the few studies examining the impact of a restrictive vs. liberal RBC transfusion strategy in children with single-ventricle physiology after cavopulmonary connection found no benefit of one over the other [100]. A major limitation of this study, however, was that the mean difference in hemoglobin between the two groups was small (hemoglobin = 11.1 g/dL for the restrictive group vs. 13.9 g/dL for the liberal group).

Current preservation techniques allow for RBCs to be stored for up to 42 days, but detrimental changes begin to occur during the storage process. This so-called “storage lesion” causes changes to the RBC membrane that alter RBC deformability and increase adhesiveness so that passage through tissue capillaries is impaired. Levels of 2,3-diphosphoglycerate decrease, resulting in an increase in the oxygen affinity of hemoglobin and decreased oxygen delivery to the tissues. Some hemoglobin molecules are converted to methemoglobin, which is incapable of binding oxygen. Finally, concentrations of nitric oxide are reduced, causing impaired tissue vasodilation. These changes result in decreased RBC viability and functionality and may result in higher rates of organ dysfunction and morbidity in patients who are transfused with older units. Indeed, several observational studies in both adults and children have suggested that prolonged RBC storage is associated with increased rates of infection, organ failure, length of hospital stay, and mortality [101,102]. Unfortunately, it is difficult in observational studies to determine whether this is truly an effect of RBC storage time or whether sicker patients simply receive more, frequently older, RBC units. The effects of this “storage lesion” can be minimized by using RBCs stored for less than 14 days [103–107]. Most pediatric cardiac centers designate younger RBC units for children with complex congenital cardiac disease.

### KEY POINTS: MANAGEMENT OF BLEEDING AFTER CPB

- Infants and especially neonates can be expected to bleed more after CPB, but preoperative laboratory tests are not helpful as predictors.
Recombinant factor VIIa
The off-label use of recombinant factor VIIa (rFVIIa) to help manage post-CPB coagulopathies in children is gaining attention. Currently, rFVIIa is only approved for use in patients with hemophilia A or B who have developed inhibitors to factors VIII or IX, patients with factor VII deficiency and, in some countries, patients with Glanzmann’s thrombasthenia who are refractory to platelet transfusions [108]. Nevertheless, it has been increasingly used outside of these indications to manage bleeding in a variety of settings, including after CPB.

Administration of rFVIIa enhances the amount of thrombin generation by saturating exposed TF in damaged blood vessel walls and enhances the rate of thrombin generation by stimulating the thrombin burst that occurs on the surfaces of activated platelets adhering to injured vessels [109]. This leads to the formation of clot with a dense fibrin structure that is resistant to premature lysis because of a concomitant increase in activation of the fibrin cross-linker, factor XIII, and thrombin-activated fibrinolysis inhibitor [110,111]. Although the administration of rFVIIa will enhance thrombin generation even in the presence of low platelet levels, the transfusion of platelets prior to its administration will improve its effectiveness [110], and the restoration of fibrinogen levels will improve the resulting clot strength [112].

No controlled trials have been performed to justify the use of rFVIIa after CPB in children, but anecdotal reports of its successful use have been reported, even during extracorporeal membrane oxygenation (ECMO). In a review of 40 pediatric publications [113], there was no substantive evidence to support the efficacy of rFVIIa as prophylactic or routine therapy during pediatric cardiac surgery. For rescue therapy (i.e., bleeding that is massive, potentially life-threatening and refractory to conventional therapy), treatment with rFVIIa may be reasonable because morbidity and poor outcome are high in children with increased transfusion requirements [96,97,114]. The fact that rFVIIa is produced using recombinant technology, thus eliminating infectious risks, makes it an appealing therapeutic option. However, its significant cost and the lack of an established safety profile limit this appeal. While enhanced thrombin generation after rFVIIa is theoretically limited to sites of vascular injury due to its required interaction with TF and activated adhering platelets, thromboembolic events have been reported after its use [108].

**Coagulation factor concentrates**
Several plasma-derived coagulation factor concentrates are available for use, including prothrombin complex concentrates (PCCs), fibrinogen concentrates, and factor XIII concentrates. They enhance coagulation by increasing the in vivo content of the coagulation factor(s) present in the concentrate. PCCs contain all the coagulation factors required to promote thrombin generation, including the vitamin K-dependent coagulation factors (II, VII, IX and X) as well as trace amounts of factors VIII, VIIa and IXa. The specific composition and amount of each clotting factor in the concentrate vary depending on the manufacturer. Approximately 15 different PCCs are manufactured worldwide. The potency of any given PCC is based on international units (IU) of factor IX activity where 1 IU is equal to the activity of factor IX in 1 mL of plasma. However, in general, the overall clotting factor concentration in PCC is about 25 times higher than that found in normal human plasma [118]. The optimal dosing of PCC is unknown, though an initial bolus of 25–30 IU/kg has been proposed to reverse bleeding associated with oral anticoagulant therapy. Others suggest different doses depending on the degree of prolongation of the INR [118]. Viral inactivation occurs during the manufacturing process to minimize the risk of pathogen transmission.
most countries both three-factor (3F) PCCs and four-factor (4F) PCCs are currently available. Three-factor PCCs contain low levels of factor VII and therapeutic levels of factors II (prothrombin), IX and X, while 4F-PCCs contain therapeutic amounts of all vitamin K-dependent factors.

Most commonly, coagulation factor concentrates are administered as replacement therapy in patients with congenital or acquired coagulation factor deficiencies. PCCs are also indicated to reverse the anticoagulant effects of vitamin K antagonists [118]. However, as with rFVIIa, coagulation factor concentrates are increasingly being administered off-label during complex cardiac surgery when conventional hemostatic treatment is inadequate.

In animal models of uncontrolled hemorrhage and dilutional coagulopathy, the administration of PCCs and fibrinogen concentrate is able to restore clot formation, reduce blood loss, and improve mortality [119,120]. There is a paucity of published human data on the hemostatic effects of these agents, particularly in pediatric patients. Despite the lack of human data, PCCs, fibrinogen concentrates, and factor XIII concentrates have all been reported to be efficacious in controlling massive intraoperative and postoperative bleeding [121–123]. One study showed that 3F-PCC was more effective at increasing thrombin generation ex vivo in neonatal plasma after CPB than rFVIIa, thus reflecting the importance of prothrombin replacement in restoring hemostasis [124]. The doses of PCC and rFVIIa used for the ex vivo model in this study were 25 IU/kg and 90 μg/kg, respectively.

The major safety concern with these agents is thrombosis. Concentrates with high prothrombin (factor II) and high factor VII activity tend to be associated with a greater thromboembolic risk [118,125]. Some manufactures have added heparin and AT or PC, or both, in an attempt to reduce the thrombogenicity of the concentrate; however, the effectiveness of this practice has not been clearly demonstrated.

### KEY POINTS: COAGULATION FACTOR CONCENTRATES

- Available concentrates include prothrombin complex concentrates (PCCs), fibrinogen concentrates, and factor XIII concentrates.
- PCCs contain vitamin K-dependent coagulation factors (II, VII, IX, X).
- PCCs are being used off-label like rFVIIa to attenuate excessive post-CPB bleeding, but little published data are available confirming their effectiveness.

### Pharmocologic therapies

#### Antifibrinolytics

Epsilon-aminocaproic acid (EACA) and tranexamic acid (TA) are the two clinically available antifibrinolytic drugs. Both exert their antifibrinolytic effect most importantly by competitively binding with the lysine binding sites of plasminogen, thus altering plasminogen’s conformation and preventing plasminogen activators from converting plasminogen into its active form, plasmin. At significantly higher concentrations, these drugs bind directly to plasmin that has already formed, thus directly inhibiting the plasmin’s activity. Both drugs are fairly rapidly excreted by the kidneys virtually intact, although TA boasts a longer half-life. TA is six to 10 times more potent than EACA [126,127].

Both EACA and TA have been shown to inhibit fibrinolytic activity when used prophylactically during CPB [64,128]. Although some postulate that fibrinolysis is not a major contributor to post-CPB bleeding [60,61,62,92], a reduction in post-CPB blood loss and transfusion requirements has been demonstrated with the prophylactic use of these drugs, particularly in adults [127–129]. The contribution of the products of fibrinolysis to the generation of post-CPB platelet dysfunction no doubt plays a role here. Indeed, studies with TA have shown not only that TA preserves platelet function after CPB, but also that the amount of postoperative bleeding correlates with the post-CPB platelet function and not with the occurrence of fibrinolysis [130].

Investigations exploring the effectiveness of EACA or TA in reducing bleeding or blood product transfusion after CPB in children have yielded conflicting results. A recent meta-analysis of antifibrinolytic use during major pediatric surgery that included 23 cardiac studies found that TA significantly reduced post-CPB blood loss in children compared with placebo. The authors were unable to comment on the efficacy of EACA because the populations studied were too heterogeneous to be pooled [131].

When analyzed separately, many studies have shown that children with cyanosis and children undergoing repeat sternotomies experience significant reductions in postoperative blood loss with the use of either EACA or TA [132–136]. Thus, these populations may provide more solid indications for the use of antifibrinolytics in the pediatric arena. It has been emphasized with both antifibrinolytics that, since the initiation of fibrinolysis begins with skin incision, administration of these drugs starting prior to skin incision results in significantly more reduction of fibrinolysis, platelet dysfunction, and blood loss than administration after CPB and protamine infusion [130,137]. Also, because of rapid renal elimination, most dosing regimens employ a loading dose followed by a continuous infusion.

Multiple dosing regimens have been reported for each of the antifibrinolytics in adult patients and subsequently extrapolated to the pediatric population. Unfortunately, few studies have actually examined the pharmacokinetics of these drugs in pediatric patients undergoing CPB. For EACA, the concentration required for maximal inhibition of fibrinolysis in adult plasma is 130 μg/mL [138]. A pharmacokinetic study of EACA in eight pediatric patients undergoing CPB, aged 9 months to 4 years, demonstrated that an initial loading dose of 75 mg/kg, a bolus dose...
to the pump prime of 75 mg/kg with an infusion of 75 mg/kg/hour was sufficient to maintain this plasma concentration in the majority of patients [139]. A very recent pharmacokinetic study of EACA in 10 neonates reported that loading dose of 40 mg/kg, infusion of 30 mg/kg/hr, and pump prime load of 0.1 mg per ml of prime volume would maintain EACA levels sufficient to prevent fibrinolysis in 90% of neonates [140].

A very recent pharmacokinetic study of TA in 55 patients 2 months-4 years of age developed recommendations for low (20 mcg/ml), intermediate (60 mcg/ml) and high (150 mcg/ml) plasma TA concentrations [141]. Recommendations varied with age; with higher loading and infusion doses in younger ages. Load to the patient varied from 4 to 120 mg/kg; infusion from 2–17 mg/kg/hr. Pump prime doses varied from 20 to 150 mcg per ml. Efficacy of these widely variable dosing regimens has not been validated. A much higher dosing protocol using a loading dose of 100 mg/kg followed by another 100 mg/kg dose in the pump prime and an infusion of 10 mg/kg/hour has proven clinically beneficial in pediatric patients [134].

Given the significant differences in the fibrinolytic system between adults and neonates, it is difficult to accept that therapeutic plasma concentrations of the antifibrinolytic agents as determined in adults should be extrapolated to the neonatal population. Indeed, for EACA, the minimal effective concentration required to completely inhibit fibrinolysis in neonatal plasma is substantially lower than that in adults, 47.8 vs. 130 μg/mL [142]. For TA, the minimum concentrations necessary to completely inhibit fibrinolysis were 6.54 μg/mL in neonatal plasma and 17.5 μg/mL in adult plasma [143]. A limiting factor is that these investigations used a very high dose of tPA in vitro, presumably much higher than normally encountered in vivo in children during CPB, to initiate fibrinolysis when determining this concentration [144]. Thus, these concentrations appear to be the maximum that would be clinically needed to inhibit fibrinolysis and, perhaps, even lower concentrations could be effective. Separate neonatal dosing regimens for EACA and TA based on these lower target concentrations have not yet been established. When doing so, pharmacokinetic data will no doubt need to be considered as neonates have a larger volume of distribution and an increased clearance in comparison to older children and adults.

Much concern has been voiced about potential thrombotic complications after the use of antifibrinolytics; however, none of the previously cited reports found any significant increase in thrombotic or embolic problems in either adults or children. These complications are of more concern when antifibrinolytics are used incorrectly during a hypercoagulable state with compensatory fibrinolysis (DIC) rather than during the primary fibrinolysis that may occur after CPB [145]. In adults, high intraoperative doses of TA have been associated with an increase in postoperative seizures [146–148]. This may be the result of TA’s ability to act as a γ-aminobutyric acid A receptor antagonist, thus inducing hyperexcitability and decreasing the seizure threshold [148].

**Aprotinin**

Prior to 2007, Aprotinin (Trasylol®; Bayer Pharmaceuticals Corporation, West Haven, CT) was commonly used during cardiac surgery in an attempt to reduce bleeding and allogeneic transfusion requirements associated with CPB. During that period, many studies in both adult and pediatric cardiac patients confirmed its efficacy in reducing blood loss and transfusion requirements [149–152]. A meta-analysis of randomized trials of aprotinin use in pediatric patients showed a 33% overall reduction in the proportion of children transfused when aprotinin was used (56% reduction in children undergoing primary sternotomies), but no significant reduction in the volume of blood transfused or the volume of chest tube drainage [153]. This effect was significant in children weighing both less than and greater than 10 kg. Studies in children undergoing repeat sternotomies documented objective reductions in transfusion requirements, time required for chest closure in the operating room, and ICU and hospital stays, resulting in financial savings despite the significant cost of aprotinin [151,154].

Aprotinin’s efficacy in neonates undergoing complex open-heart procedures has been less clear, and is supported by some but not all studies [155,156]. Much of the confusion has been created by heterogeneity in the age and weights of children receiving aprotinin, in the surgical procedures undertaken on these children, in the transfusion triggers utilized, and in the aprotinin doses used in these children as well as by the poor methodology employed in some studies [153]. In support of aprotinin, a single-center retrospective study analyzed the effectiveness and safety of aprotinin vs. a lysine analog in neonates undergoing CPB – 64% of neonates received aprotinin, 24.8% EACA and 11.2% TA [157]. The authors found that neonates receiving aprotinin had lower intraoperative transfusion requirements and shorter surgical closure times than those receiving a lysine analog. Additionally, fewer neonates in the aprotinin group required surgical re-exploration or displayed evidence of renal injury. Another comparison of aprotinin to TA in a small group of neonates undergoing CPB again demonstrated decreased postoperative transfusion requirements and attenuated inflammatory biomarkers in the aprotinin group [158]. Conversely, others have been unable to demonstrate an association between the prophylactic use of aprotinin and a reduction in blood product transfusion in neonates and infants undergoing CPB [159,160]. A large cohort study from 25 centers found no advantage of aprotinin over TA in a subanalysis of neonates in terms of bleeding requiring surgical intervention and other outcomes [160].

Although many studies addressed the efficacy of aprotinin, safety was not the primary focus, and in 2006 aprotinin’s safety profile came into question. A prospective study in adult cardiac surgical patients found a doubling in the risk of renal failure requiring dialysis among
adults who received aprotinin during primary or complex coronary artery surgery [161]. This study also reported an increase in thrombotic/ischemic-related events, such as myocardial infarction and stroke, in aprotinin-treated patients undergoing primary surgery. Also in 2006, another study in adult cardiac surgical patients reported that patients treated with aprotinin developed a higher risk of postoperative renal dysfunction during the first postoperative week [162]. In 2007, an observational study found greater 5-year mortality in adult cardiac surgery patients treated with aprotinin [163]. These concerns culminated in a multicenter, blinded, randomized controlled trial – the Canadian BART study (Blood Conservation using Antifibrinolytics: a Randomized Trial in a Cardiac Surgery Population study) [164]. Although the primary outcome in the BART trial was blood loss and transfusion requirements, it was stopped prematurely at the time of interim analysis because mortality in the aprotinin group was 3.2%, as compared with 1.7% in the EACA group and 1.3% in the TA group. The ultimate result was the suspension of aprotinin from worldwide markets by its manufacturer.

Since its publication, the BART study has been criticized for several limitations, including lack of a control group, no stratification of treatment according to procedure, and inclusion of more moderate-risk than high-risk patients [165,166]. Other studies in adults have shown no detrimental influence of the use of aprotinin on post-CPB renal function [167] or the incidence of myocardial infarction or cerebrovascular events [168]. In 2012, recognizing these limitations, Health Canada and the European Medicines Agency both independently re-examined the BART results and reinstated aprotinin into Canada’s public health system and the European Union, respectively. Despite its use in Canada and Europe, aprotinin remains unavailable for use in the United States.

Because the hemostatic derangements of CPB are more significant in pediatric patients, this population potentially stands to gain greater benefit from aprotinin’s blood-sparing effects. However, aprotinin’s safety profile in pediatric patients remains unclear. A retrospective review of aprotinin use in children undergoing CPB has found no association with acute renal failure, need for temporary postoperative dialysis, neurologic complications, or operative or late mortality [169]. Another retrospective review involving only neonates similarly showed no increase in post-CPB renal dysfunction [170] and a prospective pediatric study was not able to demonstrate an independent role for aprotinin in the development of post-CPB renal dysfunction or the need for dialysis [171]. Moreover, several pediatric studies suggest that the duration of CPB may be the more important predictor for the development of postoperative renal dysfunction [170,172]. Further studies are needed to fully determine the safety of aprotinin in children.

As aprotinin is still used in some centers, we recommend keeping several factors in mind when administering aprotinin to children. Optimal dosing protocols need to be established to achieve the desired plasma level of 200 KIU/mL in order to inhibit both plasmin and kallikrein. The risk of allergic reactions upon repeat exposures must be remembered [173]. Use of kaolin ACTs or heparin level measurements must be considered to ensure safe levels of anticoagulation with the use of aprotinin, as aprotinin itself inhibits “intrinsic” coagulation and thus may act synergistically with heparin to falsely prolong celite ACT values [174]. Currently, it remains to be seen if aprotinin will ever enjoy the wide acceptance that it had during the first 20 years after its introduction to cardiac surgery in 1987 [175].

**KEY POINTS: ANTIFIBRINOLYTICS**

- Epsilon-aminocaproic acid and TA are the clinically available antifibrinolytics in the US; aprotinin is also available in Canada and Europe as limitations in the aprotinin-critical reports have been recognized.
- Antifibrinolytics attenuate post-CPB bleeding by inhibiting fibrinolysis and preserving platelet function.
- Antifibrinolytics may be especially efficacious in neonates, cyanotic children, and children undergoing repeat sternotomies.
- Pharmacokinetic and pharmacodynamic data are lacking in children, and thus optimal pediatric dosing regimens have yet to be established.

**Blood conservation**

In recent years, the importance of blood conservation measures for pediatric open-heart surgery has received greater recognition [176–178]. Currently, utilization of blood products remains substantial, especially for infants [179]. Donor blood is a limited and costly resource with well-known associated risks. There are an increasing number of adult [180–185] and pediatric [69,78,95–97,186–194] studies reporting that blood transfusion therapy is associated with worsening patient outcomes, including greater perioperative inflammatory response, prolonged postoperative ventilation and ICU stay, and increased postoperative infections, acute kidney injury and mortality.

Blood conservation is often more successful if multiple measures are employed in multidisciplinary, collaborative, and coordinated efforts [176,177,195]. Preoperatively, the patient’s likelihood of bleeding should be assessed and a blood conservation strategy selected that has a favorable
ratio between potential benefit and risk. A variety of blood conservation strategies are listed in Box 13.1. Several of the well-established methods are discussed in the following sections and some (e.g., antifibrinolytic prophylaxis) are addressed in other sections of the chapter.

Preoperative considerations
Children become hemodiluted with the onset of CPB. The degree of hemodilution and resultant anemia depend upon the patient’s preoperative hematocrit and blood volume, the prime volume, and the desired hematocrit on CPB. A higher preoperative hematocrit increases the likelihood that the CPB target hematocrit will be achieved without recourse to PRBC transfusion.

Recombinant human erythropoietin alpha (EPO), the primary growth factor for RBCs, has been successfully employed in combination with iron supplementation as a blood conservation strategy during pediatric open-heart surgery. A report in 1997 found that EPO (300 U/kg) administered twice before and twice after surgery to children ranging in age from 3 to 13 years was effective at avoiding blood product transfusion [196]. A single EPO dose 7 days prior to surgery resulted in a non-significant reduction in allogeneic transfusions in children [197]. EPO has been incorporated into pre-donation protocols. Treatment with EPO (100–300 U/kg subcutaneously, prior to each blood donation) increased the amount of autologous blood that could be collected and minimized allogeneic blood exposure in children aged 1.2–14 years [198]. However, apart from case reports involving children from families of the Jehovah’s Witness faith [199–202], use of EPO has not been widely adopted [178]. EPO, especially when combined with autologous blood pre-donation, has probably not gained wide acceptance as a blood conservation strategy because it is resource-intensive, invasive, stressful to the patient, and not practical for urgent surgery [178].

Preoperative autologous donation (PAD) refers to the collection and anticoagulation of whole blood from a patient for anticipated perioperative transfusion. It eliminates the risk of blood-borne infections and incompatibility issues, including graft-versus-host disease, and diminishes immune modulation. The amount of blood collected from a single donation is typically limited to 10% of the child’s total blood volume. The rate of donation reactions is 2–5% and increases with decreasing age and weight. Limited venous access and patient stress from multiple procedures are additional concerns, and some centers sedate small children during blood donation. PAD is efficacious at reducing allogeneic exposure [203] but remains controversial because of issues to do with safety, cost, and the risk of delaying surgery. Suitability of PAD in children with congenital heart disease depends on the anticipated consequences upon a patient’s cardiac pathophysiology and is often limited to relatively healthy patients with simple CPB, cardiopulmonary bypass; FXIII, factor XIII; rFVIIa, recombinant activated factor VII.

*Strategies that appear to have reasonably wide acceptance among practitioners.
cardiac anomalies. Although typically reserved for older children (>7 years or > 40 kg), PAD has been reported to be useful in infants older than 6 months [204] or > 8 kg [198].

**Intraoperative considerations**

The influences of differing anesthesia techniques or agents on bleeding during pediatric cardiac surgery are poorly known. Basic principles would suggest avoidance of high blood pressure and venous congestion. Of interest, patients undergoing unifocalization of aortopulmonary collaterals may be at greater risk of hemorrhage from postoperative liver dysfunction. Intraoperative measures to preserve hepatic blood flow could be worthy of consideration.

Acute normovolemic hemodilution (ANH) is the removal of whole blood from the patient before CPB while maintaining isovolemia by crystalloid or colloid infusion and then infusing the blood after CPB. A study of 32 infants of weight 5–12 kg undergoing non-complex open-heart surgery found that ANH-treated patients had better postoperative coagulation tests and tended to receive fewer blood products (P = 0.06) than controls [205]. The CPB circuit for all patients was primed with homologous red blood cells. Factors influencing selection of patients for ANH include the patient’s hemodynamic stability and baseline hematocrit, the type of CPB prime (blood or crystalloid) and the target hematocrit during CPB. ANH may have limited application in small children because the platelets in ANH blood may be insufficient to correct severe post-CPB deficits in platelet number and function.

Platelet-rich plasma can be obtained by plateletpheresis after induction of anesthesia and transfused after CPB. There are limited pediatric studies [206] and probably very few pediatric centers utilize the technology. Current blood conservation guidelines are based on adult information and state that the use of intraoperative platelet plasmapheresis is reasonable in high-risk patients if an adequate platelet yield can be reliably obtained [207].

Fibrin glue has been used in children undergoing repair of congenital heart defects and is most efficacious in controlling low-pressure venous bleeding. Exposure to topical sealants that contain aprotinin results in an antibody response similar to that observed after intravenous aprotinin administration. When exposed to fibrin glue of bovine origin, patients may develop antibodies against bovine factor V or X that can then cross-react to inhibit the patients’ own factor V or X.

**Perfusion-related considerations**

**Hemodilution due to CPB**

Post-CPB coagulation function is greatly influenced by the hemodilution that occurs during CPB [176]. The degree of dilution depends on the patient’s blood volume, the baseline blood concentration and activity of the patient’s coagulation components (red cells, coagulation factors, platelets) and the volume and composition of the CPB circuit prime. In children, hemodilution is an independent predictor of PRBC transfusion [208] and the risk of PRBC transfusion is substantially altered by relatively small changes in prime volume. Potential benefits of small CPB circuitry include minimizing hemodilution and reducing the inflammatory response associated with CPB and blood product transfusions. Miniaturization of the CPB circuit had been reported to reduce blood product requirements, the perioperative inflammatory response, and durations of postoperative ventilation and ICU stay [69,74,78,209–218]. Techniques to reduce the CPB circuit prime volume have been reviewed and include elimination of non-essential components, using small-volume circuit components (oxygenator, filters, cannulae), decreasing the length and diameter of circuit tubing, using a remote pump head, assisted venous drainage, retrograde autologous circuit priming and microplegia techniques [177,178]. Prime volumes of 95–110 mL are reported for infants < 5 kg [178,217]. Efforts to reduce prime volumes require careful planning and meticulous management because of associated risks [177].

An important consideration is the influence of CPB-induced dilutional anemia on tissue oxygenation. Figure 13.7 illustrates the effect of differing asanguinous prime volumes on the hematocrit attained during CPB for a 3.5 kg term neonate. For example, if the neonate’s pre-CPB hematocrit is 40%, the hematocrit on CPB will be 29% for a prime volume of 120 mL, 22% for a prime volume of 240 mL, and 18% for a prime volume of 360 mL. There is debate about the lowest acceptable hematocrit during CPB. Boston investigators enrolled 217 infants who underwent biventricular repair from two randomized studies and found that a hematocrit ≥ 24% at the onset of low-flow CPB was associated with reduced lactate levels after CPB and higher Psychomotor Development Index scores at 1 year [219]. Proponents of blood conservation have argued that lower hematocrit levels are safe, particularly if mixed venous oxygen saturation, near-infrared spectroscopy cerebral and somatic oxygen saturation, and lactate levels are monitored during CPB and, if necessary, corrective measures are undertaken [177,220]. Unfortunately, all these monitors unreliable detect regional ischemia. Neurological outcomes after open-heart surgery performed at relatively low CPB hematocrit values have been reported. Ando et al. retrospectively studied 158 children < 5 kg undergoing ventricular septal defect repair who had a nadir CPB hematocrit of 15% and noted normal renal and liver function tests, no neurological deficits, and normal psychomotor development scores at 1–3 years of age [209]. A retrospective study of 70 children (58 were Risk Adjustment for Congenital Heart Surgery risk category 1 or 2) weighing approximately 5 kg with nadir CPB hematocrit values of 22% had no postoperative neurological deficits.
3.5 kg term neonate

Figure 13.7 Hemodilution with an asanguinous prime for a 3.5 kg term neonate.

and no neurological deficits at 1–3 years of age [74]. Another retrospective investigation compared 82 children who received a strategy of blood conservation with 86 historical controls who did not have blood conservation. Nadir hematocrit was significantly different between groups – approximately 22% (study) and 28% (control).

The group that received blood conservation received fewer blood transfusions and had fewer ventilator days, lower inotropic scores, and shorter lengths of stay. However, the two groups were relatively dissimilar. At the time of discharge, there were no neurological events attributed to blood conservation [220].

In summary, it is currently unknown whether hematocrit (or some other measure) can indicate when the benefits of PRBC transfusion outweigh the risks of hemodilution. The problem is complex because the effects of hemodilution may vary according to diagnosis, age at operation, CPB variables such as pH strategy and flow rate, and other perioperative factors.

Ultrafiltration
Ultrafiltration has been repeatedly demonstrated to be useful during pediatric open-heart surgery [176,221] and has become widely adopted [222,223]. Effects include hemoconcentration of the patient, removal of inflammatory mediators, and an ability to manipulate plasma electrolytes and colloid osmotic pressure. Ultrafiltration reduces the requirement for allogenic blood products by increasing the patient’s hematocrit, concentrating coagulation plasma proteins, and modulating the systemic inflammatory response to CPB [224]. Heparin blood concentration increases because it is highly protein-bound and hence not filtered [225]. There are several methods of ultrafiltration: a blood-containing CPB prime can be ultrafiltered prior to initiation of CPB; conventional ultrafiltration is performed during CPB; modified ultrafiltration (either arteriovenous or venovenous) occurs after separation from CPB and may improve hemodynamics [224,226]. The amount of ultrafiltrate obtained during conventional ultrafiltration can be increased by adding fluid to the CPB circuit to maintain isovolemia. It is unclear which of the ultrafiltration variants provides maximal clinical benefit, and many institutions perform ultrafiltration both during and after CPB [227–229]. It may be that ultrafiltration will be utilized less if CPB circuit primes are markedly reduced [178].

Cell salvage
Blood shed intraoperatively can be collected into an automated centrifuge-based blood salvage instrument that produces a heparin-free suspension of washed, concentrated RBCs. Likewise, red cells present in the CPB circuit after separation of the patient from CPB can be salvaged. Red cell salvage has been found to be a useful blood conservation technique for infants and children undergoing cardiac surgery [230,231]. Reductions in the requirement for PRBCs and other blood products was reported when salvaged blood was stored in a temperature-regulated cooler at the patient’s bedside and used for 24 hours postoperatively [232,233]. Salvaged RBCs lack plasma proteins and will lead to coagulation factor depletion if transfused in large volumes.

Unprocessed residual CPB fluid can be returned to the patient. However, this is not optimal because the fluid has a low hematocrit and contains heparin, fibrinolysis by-products, and cellular debris. Mediastinal and pleural shed blood can be collected postoperatively and reinfused, but the technique is seldom used in pediatric cardiac surgery. There is concern that reinfused shed blood
promotes a coagulopathic state because shed blood not only contains decreased amounts of coagulation factors and increased levels of fibrin degradation products but also stimulates tPA. Additionally, the hematocrit of shed blood is usually less than 20%.

Temperature regulation during CPB
Hypothermia adversely affects coagulation, and minimum core temperature during pediatric open-heart surgery has been associated with increased blood product transfusions [75]. Reduced PRBC transfusions, postoperative ventilation requirements, inotropic support, ICU and hospital stay have been reported for arterial switch procedures performed at mild rather than moderate hypothermia [234]. However, FFP transfusions were increased. Durandy reported improved patient outcomes with normothermic CPB and warm microplegia [235,236].

Other innovations
In a case series of 14 newborns with a prenatal diagnosis of congenital heart disease, autologous umbilical cord blood was harvested and subsequently transfused during open-heart surgery [237]. Perioperative homologous blood products were avoided entirely in eight of these patients.

KEY POINTS: BLOOD CONSERVATION
- Blood conservation is often more successful if multiple measures are employed in a multidisciplinary, collaborative effort.
- Preoperative methods have limited benefit and acceptance in children but potentially include the use of erythropoietin and autologous blood donation.
- Intraoperative considerations include consensus on appropriate target hematocrit, acute normovolemic hemodilution, and the use of antifibrinolytics and restrictive transfusion protocols.
- Perfusion-related efforts include circuit miniaturization, ultrafiltration, and salvage of shed blood and residual circuit volume at the conclusion of CPB.

Summary
Managing the coagulation system is an integral part of pediatric cardiac anesthesiology and surgery. Young children live with a precarious coagulation balance that is quickly disrupted by exposure to CPB. Maintenance of adequate anticoagulation during CPB, appropriate anticipation of coagulopathies after CPB, rapid diagnosis of these coagulation abnormalities, and proper use of blood products, rFVIIa, coagulation factor concentrates, and pharmacologic therapies contribute significantly to attenuating or correcting this disruption. Measures to conserve autologous blood help to limit allogenic blood product transfusions and their potential complications. Ongoing work in this field continues to enhance our ability to minimize this source of morbidity for children undergoing cardiac surgery.

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Redlin M, Kukucka M, Boettcher W, Schoenfeld H, Huebler M, Kuppe H, Habazettl H. Blood transfusion determines postoperative morbidity in pediatric cardiac surgery applying a comprehensive blood-sparing approach. J Thorac Cardiovasc Surg. 2013 Sep;146(3):537–42. This investigation reports increased morbidity in children who received perioperative blood transfusions during cardiac surgery. The paper has several limitations, but the findings are interesting and the investigators have achieved impressive success with their blood conservation strategies.
 CHAPTER 14
Preoperative Evaluation and Preparation

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Introduction

Congenital heart defects are the most common of all congenital anomalies. Every day in the United States there are 11,500 babies born, 450 of whom have a congenital anomaly, of which 87 (20%) are congenital heart defects [1]. The incidence of congenital heart disease (CHD) has remained consistent over the years and is similar across various geographic and racial and ethnic groups. Although there is a suggested increase in the prevalence of specific lesions in certain regions, the incidence is mostly 7–10/1,000 live births [2,3].

The patient with CHD

The demographics of patients with CHD are changing as screening methods evolve, diagnostic tools improve, and interventions change. Although CHD is frequently considered a disease of childhood, the population of adults with CHD is growing at a rate of 5% every year, and by the end of this decade there will be more adults than children with CHD. The congenital cardiac anesthesiologist thus has to be prepared to evaluate and care for adults as well as children with heart defects. However, there remains a significant population of neonates and infants with critical CHD who require care in the first days or months of life. In an epidemiologic study, 15% of all infants with CHD had significant physiological compromise (metabolic acidosis, seizures, cardiac arrest or evidence of renal or hepatic injury) that required an invasive intervention in the first few weeks of life [4]. Many lesions are diagnosed prenatally, and fetal interventions to improve the outcome and progress of patients are increasingly applied [5]. The interventions are also changing rapidly, and the anesthesiologist has to include in the preoperative evaluation an understanding of the planned procedure, the location, and the coordination needed between various teams. Many centers have adopted a hybrid approach to many defects, especially hypoplastic left heart syndrome (HLHS) and multiple ventricular septal defects (VSDs). These procedures will require an up-to-date understanding and preparation for those ever-changing interventions [6,7].

Terminology and classification

The primary step in the preoperative anesthetic evaluation of the patient with CHD is an understanding of the terminology and nomenclature used for these defects. The communication between various chambers and vessels is described in terms of concordance and/or discordance.
Sidedness and morphology of chambers, valves, and vessels also follow a standard description approach. To understand the nomenclature of a specific lesion, the anesthesiologist carefully considers:

- Systemic and pulmonary venous drainage
- The outlet/drainage of the atrial and ventricular chambers (e.g., a double inlet left ventricle [DILV] has both right and left atria draining into the left ventricular chamber; in a double outlet right ventricle [DORV] the right ventricle communicates directly to both the systemic and pulmonary outlets)
- Atrioventricular and ventriculoarterial communication (e.g., in congenitally corrected transposition [CCTGA] there is atrioventricular and ventriculoarterial discordance)
- The morphology of the atrioventricular and semilunar valves
- Systemic and pulmonary arterial morphology and branching.

Following an interpretation of the nomenclature and terminology, the anesthesiologist has to understand the physiologic implications of the various lesions. The most practical approach is to follow a physiologic classification for all CHDs (Table 14.1). Many CHDs that present in the neonatal period requiring urgent care are ductal-dependent lesions where a patent ductus arteriosus is essential to maintain either systemic or pulmonary flow. Defects presenting later in life or requiring later care are classified according to the presence and direction of shunting, pulmonary blood flow, and obstruction. Although there are numerous CHDs, the majority will be classified into one of four categories, with the incidence of the most commonly seen defects representing one of each of those categories [8,9]. Chapter 4 has a detailed presentation of the terminology and nomenclature of CHDs.

### Multidisciplinary approach

The preoperative period is the appropriate time to consider all the variables that can impact the preparation, planning, and conduct of the perioperative care for the child with CHD. The majority of congenital cardiac centers have a set weekly conference to discuss patients scheduled for surgical as well as catheter interventions. In that multidisciplinary conference, the history and condition of the patients are discussed, imaging studies are reviewed, and plans for any further consults or tests are investigated. The goal of the conference and the preoperative evaluation is to bring to the patient all the necessary expertise to understand the lesion, optimize the condition of the patient, and plan the best approach or intervention.

### Consent

The preoperative visit is an essential phase in preparing children with CHD and their families for the upcoming intervention. Parental knowledge, whether provided verbally, or in written or visual form has been shown to improve the parents’ involvement and effectively reduce their anxiety [10]. The purpose of the preoperative visit and the consent process is not the delivery of information and significant potential risks, but to provide the necessary knowledge to the parents (and potentially the child) of the specifics of the anesthetic procedures, the common risks and the plans to prevent or mitigate them, and the role of the various care-givers. The consent process should bring the physicians and the family together as partners with the same purpose: the best care possible and the least risk acceptable for the care of the child. Well-informed parents are able to participate in educating their child and preparing them for the intervention through therapeutic play interventions, establishing a rapport and connection.

### Table 14.1 Classification of congenital heart defects

<table>
<thead>
<tr>
<th>Category</th>
<th>Shunt direction</th>
<th>PBF</th>
<th>Most common examples</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ductal-dependent lesions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DDL for PBF</td>
<td>L-to-R</td>
<td>Decreased</td>
<td>Pulmonary atresia, tricuspid atresia, TOF with severe PS, Critical PS</td>
</tr>
<tr>
<td>DDL for SBF</td>
<td>R-to-L</td>
<td>Increased</td>
<td>HLHS, Preductal coarctation, IAA, Critical AS</td>
</tr>
<tr>
<td><strong>Common CHD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acyanotic shunt lesions</td>
<td>L-to-R</td>
<td>Increased</td>
<td>VSD (20%), ASD (16%), PDA (12%), P/CAVC (4%)</td>
</tr>
<tr>
<td>Cyanotic shunt lesions</td>
<td>R-to-L</td>
<td>Decreased</td>
<td>TOF (7%), Ebstein anomaly, PA-VSD-MAPCA</td>
</tr>
<tr>
<td>Obstructive lesions</td>
<td>No shunting</td>
<td>Normal</td>
<td>Coarctation (6.8%), AS, PS, cor triatriatum, MS</td>
</tr>
<tr>
<td>Mixing lesions</td>
<td>L ↔ R</td>
<td>Variable</td>
<td>d-TGA (3.6%), Truncus Arteriosus, TAPVR</td>
</tr>
<tr>
<td>Regurgitant lesions</td>
<td>No shunting</td>
<td>Normal</td>
<td>MR, TR, AI, PI (most post-surgical repairs)</td>
</tr>
<tr>
<td>Others</td>
<td>Variable shunting</td>
<td>Variable</td>
<td>Vascular rings, anomalous coronary lesions (ALCAPA), tumors, cardiomyopathy (IDCM, HCM)</td>
</tr>
</tbody>
</table>

DDL, ductal-dependent lesion; PBF, pulmonary blood flow; L, R, left and right; TOF, tetralogy of Fallot; PS, pulmonary stenosis; SBF, systemic blood flow; HLHS, hypoplastic left heart syndrome; IAA, interrupted aortic arch; AS, aortic stenosis; VSD, ventricular septal defect; ASD, atrial septal defect; PDA, patent ductus arteriosus; P/CAVC, partial or complete atrioventricular canal defect; PA-VSD-MAPCA, pulmonary atresia with a ventricular septal defect and multiple aortopulmonary collaterals; MS, mitral stenosis; d-TGA, dextro-transposition of the great arteries; TAPVR, total anomalous pulmonary venous return; MR, mitral regurgitation; TR, tricuspid regurgitation; AI, aortic insufficiency; PI, pulmonary insufficiency; ALCAPA, anomalous left coronary artery from pulmonary artery; IDCM, idiopathic dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy.
with the anesthesiologist. Children whose parents are better educated and informed, and who are involved in the preparation process are less anxious and more prepared for the interventions [11].

**KEY POINTS: APPROACH IN PATIENTS WITH CHD**

- Congenital heart disease is the most common birth defect requiring intervention, and survivors have increasingly complex CHD.
- Venous drainage, outlet of atria and ventricles, atrioventricular and ventriculoarterial communication, morphology of the cardiac valves, and arterial branching are crucial components of classification and nomenclature of CHD.
- A multidisciplinary planning conference for surgical patients that includes surgeons, anesthesiologists, cardiologists, intensivists, and radiologists is a key component of the perioperative care of the patient with CHD.

**Preoperative evaluation**

**History and physical examination**

An initial pre-anesthetic evaluation includes reviewing accessible medical records, ordering appropriate preoperative tests, requesting appropriate consultations, and performing a thorough history and physical examination. Although most children have undergone a thorough evaluation by their pediatric cardiologist and cardiac surgeon, the history should not only address cardiopulmonary reserve but also other multisystem co-morbidities that may affect anesthetic management. A review of the child’s medical record should assess the child’s underlying congenital heart pathology and whether that pathology is repaired or palliated; previous surgery, anesthetic experiences and complications, and diagnostic and therapeutic interventions; current medications and medication history; and drug or food allergies.

A child’s functional status will reveal information about their cardiopulmonary reserve. Functional status is assessed differently at different ages. Feeding difficulties with associated tachypnea, dyspnea, and diaphoresis with subsequent growth abnormalities and frequent pulmonary infections indicate limited cardiopulmonary reserve in the neonate and infant. School-aged children may exhibit decreased activity level or exercise intolerance with an inability to keep up with their peers, whereas older children may not only display fatigue, dyspnea, and orthopnea but may also verbalize chest pain, palpitations, and pre-syncpe or syncope. Furthermore, recent changes in baseline activity may indicate a further decline in cardiopulmonary reserve.

Recent upper (URI) and lower respiratory tract infections should be noted, as both may affect airway reactivity for 2–8 weeks [12]. Respiratory tract infections may additionally affect pulmonary vascular resistance (PVR), which may be poorly tolerated in those children with bidirectional cavopulmonary anastomosis (Glenn), total cavopulmonary anastomosis (Fontan), underlying pathology, shunt physiology, or pulmonary vascular disease. The increased risk of breath-holding, airway obstruction, and laryngospasm with subsequent changes in ventilation and oxygenation poses an increased risk to children with limited reserve [13]. Laboratory tests are available to potentially confirm the diagnosis of a respiratory tract infection. Nasopharyngeal swabs or aspirates may detect common viral infections, but, depending on the phase of the infection, may offer limited sensitivity [14]. White blood cell counts are a poor indicator of infection, especially in neonates and children with immature or impaired immune systems. Chest radiograph findings typically lag behind the presentation of clinical symptoms in children with lower respiratory tract infections and are often of little utility. Children with URIs undergoing cardiac surgery have an increased incidence of postoperative complications when compared with children without an URI [15]. Children with underlying congestive heart failure (CHF) who present with a URI pose a dilemma for the perioperative team. It may be challenging to distinguish baseline CHF symptoms as noted earlier from URI symptoms. Furthermore, although decreased respiratory reserve in children with a respiratory tract infection may place the child at risk for perioperative complications, the need for surgical expediency given the CHF may obviate the URI symptoms, and it may be prudent to proceed with surgery to prevent further progression of the CHF.

The physical examination further assesses the child’s general condition. Observation of the child during the pre-anesthetic evaluation may be the most valuable component of the physical examination. Is the child active, playful, age-appropriate, lethargic, or in failure to thrive compared with similarly aged children? Vital signs, including weight and height, heart rate, respiratory rate, blood pressure, and oxygen saturation (SpO2) should be recorded. Failure to thrive with reduced weight and height may indicate limited cardiopulmonary reserve and functional status. Blood pressure variation between extremities suggests an unexpected coarctation of the aorta. Tachypnea is one of the earliest signs of CHF. Cyanosis is usually recognized when the SpO2 is 85% or lower and is associated with unrepaired or palliated CHD from decreased pulmonary blood flow and right-to-left shunting, but children with left-to-right shunting may also have desaturation from pulmonary edema [16]. Progressive cyanosis or frequent cyanotic episodes may suggest the potential for rapid cardiopulmonary decompensation intraoperatively. Pre-ductal and post-ductal oxygen saturations should be recorded in an infant with unrepaired defect. If the pre-ductal (right arm) saturation is higher than the post-ductal saturation, deoxygenated blood from the pulmonary circulation enters the descending
aorta through a patent ductus arteriosus. This differential cyanosis may occur with persistent pulmonary hypertension of the newborn and left-heart abnormalities, such as aortic arch hypoplasia, interrupted aortic arch, critical coarctation of the aorta, and critical aortic stenosis.

The remainder of the physical examination should be a detailed evaluation of the airway, chest, and heart, with any changes from baseline noted. Wheezing and rales on lung auscultation may indicate not only reactive airway disease, chronic lung disease, or an acute pulmonary infection but also CHF. Auscultation of the heart should ideally be performed in a quiet setting with the child calm and cooperative. Heart sounds, pathologic murmurs, particularly a different murmur from previously documented, gallop rhythms, and presence of a thrill representing a palpable murmur should be noted. Hepatomegaly, jugular venous distension, and peripheral edema may indicate CHF; from either left- or right-sided pathology. Jugular venous distension is of limited value in neonates and infants, but may provide qualitative information about central venous pressure in older children [17]. Heart sounds and murmurs are influenced by patient position during auscultation as well as the period of the respiratory cycle during which the heart sound or murmur is being evaluated. Repositioning the child from supine to sitting decreases venous return suddenly and improves auscultation of heart sounds and murmurs. Innocent murmurs increase in intensity in the supine position. Diminished peripheral pulses and delayed capillary refill may indicate reduced systemic perfusion. The peripheral pulse will be reduced in the arm in which the subclavian artery to pulmonary artery shunt (Blalock–Taussig shunt) was constructed; the blood pressure will also be reduced in that ipsilateral arm. Finally, clubbing may indicate long-standing cyanosis. New or different physical examination findings from baseline necessitate further evaluation, which may include a chest radiograph, electrocardiogram (ECG), or echocardiogram.

Current and potential vascular access sites should be assessed, as it is frequently difficult to obtain access in children with CHD. Parents often have insight and knowledge about previous vascular access that can facilitate the selection of sites for potential vascular access. Children with CHD often have multiple previous arterial and venous cannulations that may result in trauma or thrombosis to those vessels. That information is additionally valuable when considering what potential sites to access. Arterial access should be avoided on the side where a Blalock–Taussig shunt was constructed as peripheral pulses and blood pressure will be reduced in that ipsilateral arm.

The airway evaluation is an essential component of the preoperative evaluation of children with CHD, particularly those with chromosomal abnormalities and syndromes. Airway evaluation should include a history of noisy breathing that may indicate airway compression from supraglottic or subglottic obstruction; for example, children with aortic arch obstruction have a 27% incidence of subglottic airway compression that becomes more symptomatic postoperatively following an end-to-side aortic arch reconstruction [18]. Previous airway history also includes previous airway interventions and complications and previous surgery to the face and neck. Airway physical examination includes assessing body mass index, patency of nares, degree of mouth opening, tongue size, palate shape and size, mandibular size, and neck mobility. Mandibular size with micrognathia and retrognathia is associated with difficult mask ventilation and intubation [19]. Many chromosomal abnormalities and syndromes that are associated with congenital heart disease, including trisomy 13, 18, and 21, DiGeorge syndrome and Turner syndrome, have an abnormal airway examination that may indicate possible difficult mask ventilation or intubation. Patients with congenital abnormalities, including pulmonary atresia, truncus arteriosus, and interrupted aortic arch are at increased risk for DiGeorge syndrome, or velocardiofacial syndrome (partial deletion of chromosome 22q11.2). All neonates and infants with reduced functional residual capacity and increased oxygen consumption require a patent airway to prevent cardiorespiratory decompensation, but children with cyanotic CHD or pulmonary vascular disease are particularly at risk of inadequate ventilation and oxygenation from a compromised airway. Previous anesthetic records should always be reviewed for any potential difficulty in mask ventilation and/or intubation along with any airway adjuncts used during mask ventilation, intubation, or extubation.

Children with trisomy 21 frequently present for surgical and other interventions at various stages of life. As these children’s age progresses, the risk of hypotonia, atlanto-axial instability and spinal cord compression increases [20]. Many centers have adopted an algorithm to approach these patients and decide on the imaging needed and the best approach to the airway [21]. The algorithm applies standard cervical spine series with flexion and extension views. An atlanto-dens interval > 4.5 mm or a neural canal width < 14 mm provides indirect evidence of cervical spine instability and will require a confirmation by magnetic resonance imaging (MRI). If confirmed, these findings in the preoperative period are significant for a high risk of atlanto-axial instability and the need for a neurosurgical consult, potential surgical fusion, or, at a minimum, a modification of airway management and intraoperative positioning.

The finding of poor laryngoscopic view, reported as a Cormack and Lehane [22] grade III or IV, is significantly higher in children with CHD, with a reported incidence of 3.5%, twice as high as the general pediatric population. This incidence was higher in patients below 1 year of age (5.6%) and in those with concomitant chromosomal and genetic abnormalities [23].

Approximately 25–40% of children with CHD may have associated anomalies, which may include neurologic, airway, gastrointestinal, hematologic, endocrine, syndrome, or chromosomal abnormalities [24]. Approximately
5–10% of children with CHD have a known chromosomal abnormality – the most common abnormalities associated with congenital heart disease are listed in Table 14.2.

**Congestive heart failure**

Similar to adults, children can have significant cardiac decompensation, resulting in poor peripheral perfusion and inability to adequately support vital organ function. Unlike adults, where CHF is most commonly caused by myocardial ischemia and dysfunction, children may have CHF despite normal myocardial vascularity and function. This may occur in the presence of significant volume overload (in shunt lesion) or pressure overload (in obstructive lesions), and frequently in patients with single-ventricular physiology, especially those with a systemic right ventricular morphology. CHF is characterized by reduced cardiac output and increased venous pressure in the systemic and/or pulmonary venous systems, often secondary to an abnormality in the myocardium. A cardiomyopathy is an abnormality of the myocardium. Cardiomyopathies are classified as dilated, restrictive, hypertrophic, arrhythmogenic, or unclassified [25]. Other causes of CHF in children include volume overload secondary to large left-to-right shunts, valvular regurgitation, and obstructive pathology. The classification of heart failure focuses primarily on the severity of illness. The New York Heart Association classification, which ranges from I (asymptomatic) to IV (heart failure with symptoms at rest), was designed for adults but may also be used for older children. The Ross Heart Classification Scale also ranges from I to IV but may be used in infants (see Table 14.3). Accurate assessment and grading of CHF in children require a consideration of age, activity, and compensatory mechanisms. Thus the revised Ross Classification has five different age groups with the scaling system (0–2) evaluating different
activities and findings per age group [26]. The Canadian Cardiovascular Society has established recent guidelines for the age-appropriate diagnosis of CHF, using commonly encountered symptoms, with recommendations for further investigations (brain natriuretic peptide [BNP], endomyocardial biopsy) and a stepwise introduction for medical therapy to optimize children with CHF prior to surgery and intervention [27].

The prevalence of heart failure-related hospitalization for children < 18 years has not changed with time, amounting to 11,000–14,000 admissions annually. In a retrospective analysis of the largest pediatric admissions database, the Healthcare Cost and Utilization Project Kids’ Inpatient Database, between 1997 and 2006, pediatric heart failure-related admissions were at the rate of 14.5–17.9/100,000 children. Although the prevalence has not changed significantly, the overall mortality is 7%, significantly higher than the overall expected mortality of 0.4% for all pediatric admissions with no, or compensated, heart disease. The hospital length of stay is significantly longer, and the outcome is clearly influenced by co-morbid conditions [28].

Children with limited cardiopulmonary reserve should be identified preoperatively as those children at highest risk of perioperative morbidity and mortality. Preoperative evaluation should include the degree and progression of symptoms and the heart failure therapy. The anesthesiologist should communicate directly with the treating cardiologist to assess the child’s functional and clinical status. Additionally, strategies and decisions for escalation of care should be discussed with the child’s parents, cardiologist, anesthesiologists, and/or intensivists. This might include the potential need for extracorporeal membrane oxygenation or other circulatory support devices. Infants with CHF often have difficulty feeding, diaphoresis with feeding, inadequate growth, and frequent pulmonary infections. Older children with CHF have symptoms similar to adults, including dyspnea at rest or exertion, orthopnea, angina, and peripheral edema. The clinical findings are similar to those seen in adults, with some variations specific to children. Common findings include tachycardia, shortness of breath, difficulty feeding, and lethargy. Hepatomegaly is frequently a characteristic sign of right-sided CHF, with edema seen in the sacral area (especially in babies) as well as the lower extremities. Left-sided CHF is manifested with pulmonary congestion, gallop on auscultation, and poor peripheral perfusion with cold and clammy skin. Children with CHF have low baseline blood pressure from the combination of diuretic therapy, angiotensin-converting enzyme (ACE) inhibitors, and beta-blocker therapy. Preoperative volume status should be assessed, as these children often have intravascular hypovolemia that is exacerbated by preoperative fasting. Children with CHF who are in-patients often have disease progression with increased perioperative risk. Those children who are treated with inotropes, vasodilators, and inodilators have the potential to deteriorate significantly with anesthetic exposure, and the ability to escalate support to maintain cardiac output is limited. BNP is a hormone that is synthesized and released into the circulation by the ventricular myocytes in response to volume expansion and increases in myocardial wall stress. The marker is useful for assessing functional status and cardiac function in those children with CHF. BNP is age- and gender-dependent, so higher BNP values are found in older female patients [29,30]. Hypoxemia directly increases BNP production and is elevated in uncorrected or palliated single-ventricle patients.

### Pulmonary arterial hypertension

Children with CHD and pulmonary hypertension are at significant risk for perioperative cardiac complications, whether in the cardiac operating room, the catheterization laboratory or for non-cardiac procedures or imaging studies [31]. The preoperative assessment can be done using the clinical presentation, imaging studies and, most importantly, cardiac catheterization information that reports the pulmonary/systemic pressure ratio and the reactivity of the pulmonary vascular bed [32]. Important information preoperatively is the response of the pulmonary vascular bed to oxygen, hyperventilation and inhaled nitric oxide and intravenous (IV) dilators. It is essential to consider the medical regimen for managing the patient, the potential benefit of additional therapy, and the safest interventions [33]. Children on multiple therapies may be unsafe to proceed with an intervention, or a procedure may preferably be done at the bedside, avoiding the triggering effects of motion, temperature change, and stimulation on PVR. Chapter 28 has a comprehensive review on the assessment, therapy, and potential outcomes for children with CHD and pulmonary hypertension.

### Table 14.3 Ross classification of congestive heart failure in children

<table>
<thead>
<tr>
<th>Stage</th>
<th>Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Intact function but recognized to have a risk factor for the development of heart failure, e.g., exposure to cardiotoxic chemotherapy or a valvular abnormality that imposes a volume or pressure overload on the ventricle</td>
</tr>
<tr>
<td>B</td>
<td>Presymptomatic state where there is discernible myocardial dysfunction, including chamber enlargement or reduced systolic function. Never had signs or symptoms of heart failure</td>
</tr>
<tr>
<td>C</td>
<td>Present or past state of symptomatic heart failure. Includes patients with New York Heart Association (NYHA) class II and III disease as well as patients who have had signs or symptoms but are asymptomatic by virtue of heart failure treatment</td>
</tr>
<tr>
<td>D</td>
<td>Advanced heart failure requiring specialized therapy such as intravenous inotropes or mechanical circulatory support</td>
</tr>
</tbody>
</table>

Source: Ross [26]. Reproduced with permission of Springer.
The neonate and premature infant

Neonates and premature infants continue to present the most critically ill group of patients with CHD requiring preoperative evaluation and urgent interventions. Early recognition and appropriate preparation result in a significant improvement in outcome. The American Heart Association (AHA) thus currently recommends routine oximetry screening on all neonates prior to discharge to prevent delayed diagnosis of critical CHD. The estimated sensitivity for detection is 70% and the risk of a false-positive screening oximetry that results in further evaluation is only 0.035% of infants screening within 24 hours of birth [34].

There is a significant negative linear relationship between perioperative mortality of preterm and near-term infants with CHD and gestational age, decreasing significantly for the same lesion as gestational age approaches 40 weeks [35]. It is also evident that the neurodevelopmental outcome, studied as various domains of language, cognition, and visual or fine motor skills up to 4 years of age, is improved in infants and children with various CHDs when delivery (spontaneous or elective/induced) is at 39–40 weeks’ gestation [36]. The preoperative preparation and multidisciplinary discussion should examine the gestational age of the fetus with CHD, and the best timing and location of delivery for a neonate with critical CHD [37].

Although small for gestational age and low birth weight are strong independent predictors of mortality in the first year of life following repair of CHD [38], delay of interventions neither compromises nor improves the outcome. For neonates < 2 kg, survival following surgical or interventional repair of CHD was determined by prenatal diagnosis (improved), type of cardiac lesion (worse), with defects including pulmonary venous malformations, and associated extracardiac defects [39].

Medications

Children with CHD are often taking numerous medications, including diuretics, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs) beta-blockers, anti-arrhythmics, and digoxin. These medications should be continued preoperatively until the time of the surgical procedure. Reports in the adult literature suggest that ACE inhibitors and ARBs may cause prolonged hypotension during anesthetic induction and should be discontinued at least 24 hours prior to the surgical procedure [40]. Digoxin is discontinued 24 hours prior to the surgical procedure, as serum levels may be potentially toxic postoperatively [41,42]. The American College of Chest Physicians recently published guidelines for antithrombotic therapy in children [43]. Children with systemic-to-pulmonary artery shunts, a history of shunt or conduit thrombosis, mechanical or biological prosthetic heart valves, transcatheter interventions or device placement, treatment of Kawasaki disease, and risk factors for thromboembolic phenomenon, such as bivacal pulmonary anastomosis, are often taking antithrombotic therapy. No specific guidelines exist for discontinuation of antithrombotic medications prior to elective surgery in children. Aspirin irreversibly inhibits cyclooxygenase for the life of the platelet, approximately 10–14 days [44]. Clopidogrel also irreversibly inhibits platelet aggregation. A child taking preoperative aspirin and/or clopidogrel to maintain shunt patency should continue these medications, as the risk of shunt thrombosis is greater than the risk of perioperative bleeding. Immediately discontinuing aspirin preoperatively does not reduce the risk of perioperative bleeding, given aspirin’s long half-life. There should be a discussion with the child’s cardiologist, surgeon, and anesthesiologist regarding the optimal timing for stopping these medications. Children who are taking warfarin for their antithrombotic medication should discontinue the warfarin 3–5 days prior to the surgical procedures. The international normalized ratio will usually fall below 2.0 in approximately 2–3 days and will normalize in 4–6 days [45]. Patients should be admitted 2–3 days prior to the surgical procedure to start a bridging regimen of IV heparin. Cessation of the IV heparin 3–6 hours prior to the surgical procedure does not increase the risk of perioperative bleeding [46].

Prostaglandin E₁ (Alprostadil) maintains ductal patency in ductal-dependent lesions, such as pulmonary atresia with or without VSD, tricuspid atresia, HLHS, interrupted aortic arch, or severe coarctation of the aorta. The dose, usually between 0.0125 and 0.1 μg/kg, is adjusted according to the neonate’s weight and renal function in order to maintain appropriate oxygenation without signs of over-circulation, decreased systemic diastolic blood pressure, and appropriate acid–base status. Common side-effects of prostaglandin E₁ infusion include apnea, fever, flushing, tachycardia or bradycardia, and platelet dysfunction; rarely, cardiac arrest can occur, with the prostaglandin being a contributing factor.

Children who have undergone heart or lung transplantation are often taking multiple immunosuppressive medications that should be continued through the perioperative period to reduce the risk of acute rejection. Finally, children who are taking other medications, such as those for reactive airway disease, gastroesophageal reflux, and seizure disorder, should continue these medications until the surgical procedure.

Electrocardiographic evaluation, pacemakers, and defibrillators

Children with CHD frequently have rhythm disturbances that require anti-arrhythmic therapy and are manifest on a preoperative ECG. A 12-lead ECG with adequate length of lead II recording for diagnosis of arrhythmias and assessment of changes from baseline is an important component in the evaluation for cardiac surgery. Even if it is “normal” (i.e., normal sinus rhythm without evidence of chamber enlargement or repolarization abnormalities, etc.), the formal 12-lead ECG serves as a comparison to the postoperative state if ECG changes are suspected and thus should be obtained before any cardiac surgery. If the patient has a history of significant arrhythmia, or suspicion for changing
rhythm status, a 24-hour Holter monitor is an extremely valuable test to assist in planning for management of cardiac rhythm during the procedure. Chapter 18 presents an extensive discussion of ECG and arrhythmia analysis and treatment.

Pacemakers and implantable cardioverter defibrillators, collectively referred to as cardiac rhythm management devices (CRMDs), are commonly used in children with CHD due to either congenital, acquired or iatrogenic rhythm disturbances. These devices may be placed temporarily (postoperatively) or as permanent devices due to intrinsic heart disease (common with CCTGA and cardiomyopathies) or they may be acquired following cardiac operations due to scarring, patches, and morphologic chamber changes (as with repaired tetralogy of Fallot). The preoperative period is a critical time to prepare the child with a CRMD for a safe perioperative period. The primary step is to obtain a detailed history of the indication, timing, and type of device placed. Devices have a standard nomenclature established by the North American Society of Pacing and Electrophysiology (NAPSE). An understanding of the position/nomenclature used is essential: I, chamber (s) paced; II, chamber(s) sensed; III, response to sensing; IV, rate modulation; V, multi-site pacing capability. It is important to obtain an ECG to identify pacer spikes and rate, and a chest radiograph to examine the location of the generator and the pacing leads/wires. The CRMD should be interrogated by a programmer, a manufacturing consultant, or an electrophysiologist and its battery life examined [47]. Children are more vulnerable than adults to faster battery generator utilization (due to heart rate) or dislodged/fractured leads (growth changes) or to receiving inappropriate shocks, as shown in a large pediatric CRMD series [48]. The CRMD should be reprogrammed for elective surgery to an asynchronous mode at a rate appropriate for the age and metabolic demands of the patient and the planned procedure, with all anti-tachycardia function turned off. The location of the generator must be clearly marked and noted to plan the necessary approach to avoid or limit the electromagnetic interference intraoperatively [49]. For urgent or emergency procedures, a magnet may be placed on a CRMD to revert the device to a fixed rate, asynchronous pacing mode where no cardiac activity is sensed. Caution must be used when applying a magnet, as the preset rate may not be sufficient for the metabolic demands, and may be dependent on the battery voltage and life of the generator. A regular 90 Gauss magnet will deactivate the anti-tachycardia function of an implantable cardioverter defibrillator, but not reset an asynchronous pacing mode. Thus, for all children with a CRMD, whether the device is reprogrammed or a magnet is used, perfusion must be monitored with a waveform monitoring device (pulse oximeter or arterial line wave) throughout the operative procedure until the magnet is removed or the device is interrogated and reprogrammed [50]. Chapter 18 contains a detailed discussion of the management of CRMDs.

**KEY POINTS: PREOPERATIVE EVALUATION**

- A detailed history of cardiac symptoms, diagnostic and therapeutic procedures, and complications is crucial for peri-anesthetic planning.
- Non-cardiac problems, such as genetic or dysmorphic syndromes leading to difficult airway management, are frequently encountered in the CHD population.
- Congestive heart failure, pulmonary hypertension, neonatal and premature patients, medication management, and pacemakers and defibrillators all deserve special attention in CHD patients.

**Laboratory evaluation**

Standard laboratory testing for all children undergoing cardiac interventions must include an assessment of the hematologic status, coagulation testing, serum electrolytes, and kidney function tests (creatinine and blood urea nitrogen [BUN]). Liver function tests (bilirubin, aspartate aminotransferase and alanine aminotransferase) are assessed when there is suspicion of hepatic dysfunction. Preparation of components for blood transfusion is essential and will require antibody screening and cross-matching. The hemoglobin concentration may reveal anemia and necessitate priming of the cardiopulmonary bypass (CPB) circuit with red blood cells. Children with chronic hypoxemia have significant hematologic consequences. Chronic hypoxemia increases erythropoietin activity, increasing hematocrit, hemoglobin, and viscosity, and allowing increased oxygen delivery without a sustained increase in cardiac output. However, oxygen delivery can be reduced from red cell rigidity if the hematocrit exceeds 65% [51]. Hyperviscosity is associated with cerebral arterial and sinovenous thromboses, particularly in those children who are dehydrated, have fever, or have iron deficiency. All children with chronic cyanosis should have a preoperative hemoglobin and hematocrit. Hematocrit > 60% is an indication for preoperative IV fluid therapy. Preoperative phlebotomy is not advocated unless the child is experiencing severe symptoms of hyperviscosity syndrome, such as headaches, dizziness, impaired mental status, visual disturbances, muscle weakness, or paresthesias in the absence of dehydration or iron deficiency [52]. Repeat phlebotomies have been shown to increase the risk of cerebrovascular accidents by causing chronic iron deficiency, resulting in microcytosis and increased blood viscosity. Volume resuscitation and iron replacement therapy should be started prior to elective phlebotomy. Approximately 20% of children with polycythemia have other abnormal hematologic laboratory tests, including prolonged prothrombin and thromboplastin time, thrombocytopenia, platelet dysfunction, hypofibrinogemia, and accelerated fibrinolysis [28]. Furthermore, all children with CHD undergoing CPB are at risk for intraoperative
and postoperative hemostatic derangements. A baseline platelet count, prothrombin time, partial thromboplastin time, and fibrinogen level should be evaluated preoperatively in all children. A screen for antibodies and a cross-match for red blood cells should be performed to ensure that compatible blood is available, particularly for a child who may have had prior exposure to blood products and developed serum antibodies.

Serum electrolytes should be evaluated in children taking diuretics or ACE inhibitors, as both may result in significant imbalance in the metabolic state. Neonates and infants are at risk for both hypoglycemia and hypocalcemia [53]. This is more prevalent in patients with specific syndromes (as Beckwith–Wiedemann) and those receiving parenteral nutrition. Signs and symptoms of hypoglycemia and hypocalcemia are subtle in neonates and infants, including jitteriness, fussiness, tachypnea, and tachycardia. Children with DiGeorge syndrome, with abnormal parathyroid gland dysfunction, are at risk for perioperative hypocalcemia and should have a preoperative calcium level evaluated. They are also at risk for infections due to immune-deficiency and will require irradiated blood products whenever needing a transfusion. Children with Down syndrome have an approximately 10% incidence of congenital or acquired thyroid dysfunction and should have preoperative thyroid function tests performed [54]. Preoperative arterial blood gases may reflect the degree of cardiopulmonary reserve. An arterial PaO$_2$ of 30–40 mmHg and peripheral O$_2$ saturation < 70% may indicate poor cardiopulmonary reserve. Metabolic acidosis, assessed from base status, anion gap, and lactate, reflects maldistribution of cardiac output, particularly in those children with ductal-dependent systemic circulation and CHF. Preoperative BUN and creatinine should be assessed in those children who are at risk for reduced systemic perfusion and perioperative renal impairment.

**KEY POINTS: LABORATORY EVALUATION**

- Hemoglobin level is a key preoperative laboratory value, with elevated levels indicating compensatory response to chronic hypoxemia.
- Platelet count, prothrombin and partial thromboplastin times, and fibrinogen level should be obtained before cardiac surgery.
- Electrolytes and BUN/creatinine should be assessed in patients on diuretic therapy.
- Other laboratory tests are guided by signs/symptoms, and previous history of organ dysfunction (e.g., hepatic, hypoglycemia, hypocalcemia).
- A 12-lead ECG is an important diagnostic tool before cardiac surgery.

**Preoperative imaging studies**

Imaging is essential to identify subjects with CHD, to establish the need for treatment and the optimal mode of treatment, to define anatomy and hemodynamics for treatment planning, to monitor for complications after treatment, and to determine the appropriate timing of repeat intervention. In the preoperative period, imaging is required to assess pulmonary vascularity, clarify hemodynamic status, confirm cardiovascular anatomy, determine airway patency, assess position of vital catheters and tubes, and screen for acute conditions such as hemorrhage, edema or infection. Commonly used imaging modalities include chest radiography, echocardiography, cardiac catheterization, MRI, and computed tomography (CT).

All imaging modalities should be considered important in the preoperative evaluation, preparation and decision-making. A clear example is the assessment of the child with CHD and pulmonary hypertension, where all investigative procedures contribute important information for the evaluation of the degree, reactivity, and risk of pulmonary hypertension [55].

**Chest radiography**

In an era of advanced technology and the availability of much more effective imaging modalities, chest radiography may not be carried out. However, the careful review of a preoperative chest radiograph is essential for the best preparation of a patient with CHD scheduled for a cardiac intervention.

The chest radiograph can provide pertinent information about cardiac size and chamber enlargement. A significant increase in the cardiothoracic ratio (>0.5) reflects cardiomegaly, which can be due to increased volume load to a cardiac chamber, valve regurgitation, or poor function with cardiac dilatation. A careful examination of the bronchovascular markings and lung fields can differentiate between children with significant increase in pulmonary blood flow and those with obstruction to flow due to either anatomic or physiologic etiology with increased PVR [56] (Figure 14.1).

The chest radiograph also provides information on the airway, especially in patients with risk of airway obstruction from vascular compression (enlarged pulmonary arteries, aneurysmal aortic dilation, Kommerell diverticulum) [57].

The surgical and anesthesia teams must review the chest radiograph prior to any repeat sternotomy, to prepare for the potential risk of vascular structure injury during dissection. A narrow retrosternal space on lateral radiograph reflects an adherent vascular anatomy with risk of injury to the innominate vein, right ventricle, or a pulmonary artery conduit [58].

Similarly, chest radiographs provide information on the location of vascular lines (especially umbilical catheters in neonates), which can help with the decision to use them during the procedure for valid pressure monitoring and various medication infusions. Umbilical venous lines located in the hepatic silhouette may not have passed through the ductus venosus and carry the risk of portal vein thrombosis [59]. Using umbilical artery catheters for blood pressure monitoring and blood gas sampling
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Figure 14.1 Chest radiography. (A) Newborn with dextro-transposition of the great arteries, egg-on-string appearance of the cardiac silhouette and increased pulmonary vascularity. (B) Newborn female with tetralogy of Fallot, ventricular septal defect, pulmonary atresia, ductal-dependent pulmonary blood flow, and decreased pulmonary vascularity. Note the skeletal abnormalities (VACTERL syndrome).

carries significant risk of renal artery thrombosis and lower extremity emboli, if present at or below the renal arteries, and should ideally be identified at the level of the third lumbar vertebra on chest radiography [60,61].

Echocardiography

Transsthoracic echocardiography (TTE) has long been considered the gold standard in evaluating neonates and children with CHD prior to cardiac interventions. The feasibility of obtaining clear images with multiple acoustic windows, easy access, minimal need for sedation, and low risk results in TTE being the most common imaging tool in the preoperative period. Most anatomic diagnoses can be obtained confidently with TTE, and the reporting process has become well standardized to provide the anesthesiologist in the preoperative period with information on structural abnormalities, function, chamber size as well as physiologic parameters.

The anesthesiologist should consider the echocardiographic parameters used to evaluate a specific lesion preoperatively, to clearly understand the anatomy and the degree of decompensation, and to plan the best approach for the intraoperative care. Following a stage I repair of HLHS, infants are at risk for recoarctation of the aorta (in 20% of patients) at subsequent stages of repair. There are useful TTE parameters for evaluating recoarctation, including peak isthmus velocity > 2.5 m/s and coarctation index (ratio of the narrowest region of the descending thoracic aorta to the distal descending aorta diameter) < 0.7, which can guide the preoperative risk assessment [62].

A review of TTE to evaluate ventricular function is important, especially in the presence of confounding variables that can bias the estimation of function, such as valvular regurgitation with a large ejection fraction. In patients with significant mitral regurgitation, ventricular dysfunction may be difficult to assess in the preoperative evaluation. Useful echocardiography tools include an attention to the regurgitant fraction, the effective ejection fraction, and a higher E/E’ ratio (ratio of mitral peak velocity to early diastolic velocity of the mitral annulus), which are associated with increased mortality and adverse outcome [63].

An understanding of the morphologic parameters that identify a borderline left or right ventricle is important in the preoperative evaluation of children with CHD. In children with a hypoplastic tricuspid valve, and a borderline right ventricular chamber, parameters including atrioventricular valve index (right-to-left atrioventricular valve area < 0.5) and right/left ventricular length ratio (<0.7) are useful in the preoperative preparation (Figure 14.2) [64,65].

However, although a reliable tool in many circumstances, TTE has its limitations. Inter-observer variability in the interpretation of echocardiographic findings affects

Figure 14.2 Echocardiography: 3-year-old with hypoplastic right ventricle, small tricuspid annulus and an atrial septal communication (RV, right ventricle; LV, left ventricle; ASD, atrial septal defect; RA, right atrium; LA, left atrium, TV, tricuspid valve).
agreement on anatomic as well as functional data, and can significantly impact the planned intervention as well as the extent of anesthetic preparation. Echocardiographic prenatal diagnosis of CHD can have up to 50% variability of anatomic detection of defects [66]. The interpretation of function can also vary significantly among investigators using current guidelines. In a study of 175 children with dilated, hypertrophic and restrictive cardiomyopathy, agreement among investigators on the grading of diastolic dysfunction was poor (<36%) due to the large range of normal pediatric reference values [67]. The diagnosis of left ventricular endocardial fibroelastosis (EFE) and non-compaction (LVNC) can also be challenging. In a series of 104 children with LVNC preoperatively, the agreement between observers on the number and degree of trabeculations was < 60%, and on the absolute diagnosis of EFE/LVNC was < 67% [68]. Chapter 12 has a complete review on echocardiography applications and limitations in CHD.

**Cardiac catheterization**

In the current era, it is rare to use cardiac catheterization for the primary diagnosis of CHD or for the evaluation for operative interventions. The majority of catheterizations in children are performed for interventions, or to complete and complement a difficult diagnosis, providing additional information to other imaging modalities. Many children with single-ventricle physiology can undergo staged repair without cardiac catheterization [69], with reliance on information from less invasive studies such as echocardiography and MRI. However, there remains a subset of children in whom evaluation of the branch pulmonary arteries or the reconstructed aortic arch is insufficient with TTE or MRI, and cardiac catheterization is integral in the preoperative evaluation [70].

Similarly, the evaluation of children with idiopathic or CHD-related pulmonary hypertension is critical in the preoperative preparation of these patients. The anesthesiologist should review the catheterization report for the degree of increased PVR, the ratio of right/left ventricular pressure and the response to pulmonary vascular dilators, most importantly oxygen and nitric oxide inhalation. Patients presenting with catheterization data showing a pulmonary artery pressure > 50% of systemic arterial pressure, a PVR of > 4 Wood units, and a failure to respond to vasodilator therapy are of significant risk in the perioperative period [71].

The anesthesiologist must review the catheterization report, to learn information regarding the complete anatomic diagnosis, associated anomalies, shunt direction and degrees, pressures and gradients, and ventricular function [72]. A demonstration of the value of a catheterization report is presented in Figure 14.3 showing a child with pulmonary atresia and intact ventricular septum who had undergone several staged repairs. The catheterization report can identify important preoperative information, including tricuspid annular size, presence of right ventricular dependent coronary fistulae, and bidirectional Glenn pressure, all of which have prognostic value. The degree and direction of shunting across the atrial septum can be assessed from the stepwise changes of saturation between chambers provided in the catheterization report.

A complete review of cardiac catheterization indications, interpretation, and anesthetic management is presented in Chapter 29.

**Magnetic resonance imaging**

Magnetic resonance imaging plays an important complementary role to echocardiography in the evaluation of cardiac morphology and function in children with CHD in the preoperative and postoperative periods. Recent technological advancements including free breathing capabilities, improved image resolution, ultra-short imaging time, and real-time imaging, along with a burgeoning trained user-base, increasing accessibility to MRI scanners, a steady stream of clinical validation studies, and a lack of ionizing radiation have all combined to significantly expand the indications for MRI in pediatric cardiovascular disease over the past several years. Most patients under the age of 8 years who undergo a cardiac MRI study will need either IV sedation or general anesthesia with endotracheal intubation. Endotracheal intubation, often with pharmacologically induced muscle relaxation, is needed if breath-holding is desirable. IV sedation is a preferred alternative to intubation among parents and many anesthesiologists, but has two important requirements: anesthesiologists experienced in administering IV sedation in patients with CHD; and the ability to modify the MRI sequences for free breathing acquisition.

Cardiac MRI is a dynamic user-dependent examination, and changes to the protocol will be needed based on real-time evaluation of the initial sequences. The pulse sequences used include [73]:

- **Black-blood sequences** – these provide multi-slice static images, with excellent spatial resolution with thin slices even in neonates. They provide an overview of vascular anatomy, spatial chamber relationships, airway morphology, and abdominal visceral anatomy, and form an important part of the preoperative evaluation.

- **Bright-blood sequences** – these sequences have excellent temporal resolution, allowing multi-phase evaluation across the cardiac cycle, and optimal myocardial and blood pool contrast. They are used for ventricular functional assessment and to evaluate valvular morphology and intracardiac morphology, to determine veno-atrial connections, and to track the course of the extracardiac vasculature. Alternatively, free-breathing whole heart coverage utilizing a three-dimensional steady-state free precession (3D SSFP) sequence with respiratory navigator gating has been used to provide comprehensive static, high-resolution morphologic bright-blood evaluation of intracardiac morphology and extracardiac vascular anatomy in one sequence.
Figure 14.3 Cardiac catheterization diagram of the patient in Figure 14.2 showing anatomy, pressure, and resistance measurements. BSA, body surface area; Hb, hemoglobin; Hct, hematocrit; Qp:Qs, pulmonary to systemic blood flow ratio; Rp:Rs; pulmonary to systemic resistance ratio; PAR, pulmonary artery resistance, Wood units; SVR, systemic vascular resistance; Qp, pulmonary blood flow; Qs, systemic blood flow; ABG, arterial blood gas. A, atrial A-wave pressure; V, atrial V-wave pressure; M—mean pressure. RPCW, right pulmonary capillary wedge pressure (mm Hg); LPCW, left pulmonary capillary wedge pressure (mm Hg). Circled numbers are measured oxyhemoglobin saturations, uncircled numbers are pressures in mm Hg. Numbers followed by mm are diameter measurements.

- **Flow velocity mapping** – this is accomplished by a gradient echo-based pulse sequence known as phase contrast. Phase contrast imaging is based on the principle that moving protons, such as those in flowing blood, when experiencing a specific bi-polar gradient, will accumulate a predictable phase shift that is proportional to their velocity. Phase contrast imaging can be used to quantify stroke volume, valvular regurgitation, Qp/Qs, differential pulmonary artery flow, venous return, coronary flow, and pressure gradients across stenoses using the modified Bernoulli equation.

- **Magnetic resonance angiography** – the most common sequence used is the contrast-enhanced magnetic resonance angiography (CEMRA) performed in dynamic fashion following bolus injection of gadolinium, providing a high-resolution three-dimensional (3D) dataset, with its main application being evaluation of the extracardiac thoracic vasculature, including the pulmonary arteries, pulmonary veins, aorta, systemic veins, and collateral blood supply to the lungs. Techniques of post-processing include multi-plane reformatting, maximum-intensity projection, volume rendering, and virtual angioscopy. Gadolinium contrast agent has recently been discovered to be associated with development of nephrogenic systemic fibrosis, predominately in adult patients with acute or chronic renal failure. Therefore, thoughtful determination of the benefits and risks in children with CHD is essential.

Use of MRI has been primarily to define anatomy that is problematic to image using two-dimensional echocardiography, including stenotic branch pulmonary arteries, abnormal pulmonary venous drainage, aortic coarctation, complicated 3D interrelationships, and vascular rings. MRI is the non-invasive gold standard for measurement of ejection fraction, ventricular volumes, regurgitant fraction, differential pulmonary blood flow and Qp/Qs. The major benefit of MRI compared with other imaging modalities is the complete avoidance of ionizing radiation. Image quality for echocardiography is also limited in older children due to less optimal ultrasound windows because of larger distances with growth; many children have also had previous cardiac surgery, which may affect images due to scar tissue and distortion of anatomic relationships. Particularly in older children or adults who do not require
sedation, MRI can be another option for imaging, often adding important benefits beyond echocardiography. Unlike echocardiography, MRI is not done to determine the initial cardiac anatomy, but is utilized for the imaging of regions that are more problematic to quantitatively evaluate with echocardiography, including right ventricular ejection fraction and flow into the pulmonary circulation. Perioperative utility of MRI includes an important role in determining the timing of surgery for some lesions. Repeated measurement of right ventricular volume, ejection fraction, and pulmonary regurgitant fraction is now an important tool in decision-making regarding the timing of pulmonary valve replacement after tetralogy of Fallot repair; a right ventricular volume of 170 mL/m² or more is an indication for valve replacement used by many institutions [74]. Before superior cavopulmonary anastomosis and Fontan operations (Figure 14.4) MRI is becoming essential for non-invasive imaging of the status of the right and left pulmonary arteries, pulmonary veins, aortic arch, atrioventricular valves, and ventricular function apart from venous and aortopulmonary collaterals [75]. If interventional catheterization procedures are not required before these operations, MRI is increasingly used in lieu of cardiac catheterization to obtain anatomic information as well as some functional data to plan the surgery.

**Computed tomography**

Congenital heart disease is one of the areas that has benefited tremendously from advances in CT technology. The scientific literature of the 1980s and early 1990s describes the use of helical CT mainly for anomalies involving the great vessels, including diagnosis of pulmonary and systemic venous anomalies, coarctation, and vascular rings. Today, ECG-gated multi-detector CT is the non-invasive gold standard for coronary artery imaging, and has been used for evaluation of cardiovascular morphology, myocardial wall motion and function, valvular morphology and function, myocardial perfusion and viability, vessel wall characterization, postoperative changes and stent patency [76]. It is considered an important complementary modality to echocardiography and MRI for all forms of heart disease.

Multi-slice CT has evolved rapidly, and 64-slice CT has now become commonplace, with 256- and 320-detector scanners beginning to appear on the market. A multi-slice CT with x detectors can obtain x times more data per revolution than single-slice spiral scanners. The modern CT scanners also have gantries that spin faster than three revolutions per second, further increasing the speed of data acquisition. The increased speed could be traded, if desired, for improved longitudinal resolution, increased volume of coverage, or improved image quality. This allows for considerable flexibility in CT protocols, especially in small children who cannot lie still, or cannot suspend respiration.

Sedation is most often not required for ultrafast CT sequences, in contrast to MRI, which requires at least sedation, and often general anesthesia in young children. The disadvantage of CT is that ionizing radiation exposure
occurs in all cases, and IV contrast is necessary in most. If there is one factor that limits widespread utilization of CT in pediatric patients, it is concern regarding radiation exposure. Although the risk posed by radiation from CT is minimal, it is real and must be balanced against the benefits of the examination. When performed for appropriate indications with proper technical parameters, especially in newer generation scanners, the benefits far exceed the very small individual risk. Besides strictly limiting the indications for pediatric CT to those in which diagnostic information cannot be obtained from an alternative non-radiation imaging modality such as echocardiography or MRI, there are several means of decreasing the radiation dose, including confining the study to the anatomical region of interest, using a volumetric technique rather than a helical technique, using a larger pitch, decreasing the tube current (mA) to a minimum, shielding of sensitive areas such as the breast, thyroid, gonads, bone marrow and the eye, avoiding the need for repeat examinations by attention to meticulous technique, including use of proper immobilization and sedation, and restricting the dose-intensive retrospective ECG-gated approach to a few indications which require such a technique, such as coronary artery stenosis imaging. Most questions in pediatric cardiac imaging can be answered with prospectively ECG triggered or un-gated studies, which have significantly lower radiation exposure than retrospectively gated studies.

A number of new applications, covering almost every part of the body, have evolved based on the major advantages offered by the multi-detector scanners: improved volume coverage, temporal resolution, and spatial resolution. Some of these applications include coronary imaging, evaluation of aortopulmonary collaterals in pulmonary atresia (Figure 14.5), ventricular function, high-resolution imaging of the lungs, and dynamic airway imaging (Figure 14.6) [77].

**Choice of echocardiography, CT, or MRI for non-invasive assessment of CHD**

Echocardiography plays a central role in the non-invasive delineation of CHD at all ages. The failure rate with echocardiography increases in the postoperative setting and in older children, when acoustic windows diminish. In the preoperative period, there are numerous examples involving the extracardiac vasculature, in which the lack of optimal acoustic windows results in inadequate characterization of pathology by echocardiography. These include aortic coarctation, anomalous pulmonary veins, scimitar syndrome, systemic venous anomalies, branch pulmonary artery stenosis, and anomalous coronaries. The role of MRI and CT in characterizing the extracardiac vasculature in such patients is well established [78]. On the other hand, echocardiography is quite successful, in the vast majority of cases, in delineating the intracardiac pathology, including atrial, ventricular and great arterial situs, the segmental connections, ventricular function, the status of the atrial and ventricular septum and the cardiac valves. But, even in expert hands, some intracardiac defects remain difficult to diagnose by echocardiography. There are an increasing number of papers in the literature addressing the role of MRI as a troubleshooting modality in such situations. A good example is decision-making regarding single- vs. biventricular repair in children with borderline hypoplasia of the left ventricle, in which ventricular volumetry using
MRI complements the assessment of intracardiac anatomy by echocardiography. In a series of 154 neonates with left-sided obstructive lesions and a borderline left ventricular volume that underwent an acceptable biventricular repair, only 8% had echocardiographic inclusion criteria to have a good long-term outlook after repair [79]. Echocardiography consistently underestimates left ventricular volume, compared with MRI, and may unfairly preclude some patients from a biventricular repair pathway [80].

Imaging with MRI and CT plays an important role in the postoperative setting when echocardiography windows typically diminish. Examples include tetralogy of Fallot, complex two-ventricle repair, and single-ventricle repair. The goals of postoperative imaging are assessment of ventricular and valvular function, surveillance of grafts, conduits and baffles, early detection of complications, and determination of timing of repeat surgical intervention.

Magnetic resonance imaging enjoys a clear superiority over CT for evaluation of intracardiac anatomy, flow, and function. But in situations where the clinical question is restricted to the morphology of the extracardiac vasculature, including the coronaries, pulmonary arteries, aorta, and pulmonary or systemic veins, CT is comparable to MRI (Figure 14.7). Examples of indications appropriate for CT include, but are not limited to, evaluation of total or partial anomalous pulmonary venous return, pulmonary vein stenosis, systemic and pulmonary venous anatomy in heterotaxy, branch pulmonary artery stenosis, confluence and size of branch pulmonary arteries and presence of systemic-pulmonary arterial collaterals in pulmonary atresia, vascular rings, anomalous coronaries, and the presence and severity of coarctation. While MRI provides a more comprehensive evaluation of cardiac form and function in these patients, including calculation of ventricular volumes and function, Qp/Qs, differential pulmonary flow, gradient estimation, and quantification of valvular regurgitation, it is uncertain if the additional information provided by MRI alters clinical decision-making.

There are a few instances where CT is indispensable, as in the presence of pacemakers, aneurysm clips, vascular coils, clips, and stents, and thoracic scoliosis rods. CT has the potential to assess patency of stents or metallic prostheses placed across pulmonary arteries, baffles, coronary arteries, and aortic branches. The spatial resolution of CT is superior to MRI, with the ability to reconstruct up to 0.3 mm in the z-axis. Studies have shown that CT is superior to MRI for the evaluation of coronary artery stenosis. One important advantage of CT angiography,
Figure 14.7 Electrocardiogram-gated computed tomography (CT) angiography of the heart in an 18-year-old female with infective endocarditis of the aortic valve, and left ventricular outflow tract (LVOT) pseudoaneurysm. (A) Transverse image at the level of the LVOT below the aortic valve demonstrating a 25 × 24 mm wide mouth, and extending into the mitral-aortic intervalvular fibrosa. A, ascending aorta. (B) Axial contrast-enhanced image of the upper abdomen demonstrating multiple wedge-shaped hypodensities within the spleen, representing small embolic infarcts. (C) Coronal LVOT view demonstrating thickened aortic valve leaflets (Ao V) and bulky irregular rotations involving the right leaflet. (D) Lateral projection from a three-dimensional volume rendering demonstrating the large subvalvular pseudoaneurysm of the LVOT (pink arrow). CT is helpful for evaluation of the emergent conditions, offering high-resolution imaging of the heart and vasculature without the need for sedation or breath-holding in most cases, and reduces to time spent in the imaging suite. A, ascending aorta.

Table 14.4 Computed tomography (CT) and magnetic resonance imaging (MRI) in congenital heart disease

<table>
<thead>
<tr>
<th></th>
<th>CT</th>
<th>MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Need for sedation</td>
<td>With new generation scanners, sedation is needed only in a minority of cases, but with 64-slice or older scanners, most children &lt; 5 years need sedation</td>
<td>Required in almost all patients &lt; 8 years, and most patients &lt; 11 years</td>
</tr>
<tr>
<td>Duration of sedation</td>
<td>Very short</td>
<td>Long</td>
</tr>
<tr>
<td>Intravenous contrast</td>
<td>Excellent safety record, but risk of allergic reaction, renal dysfunction, extravasation</td>
<td>No risk of allergic reaction or renal dysfunction</td>
</tr>
<tr>
<td>Spatial resolution</td>
<td>Better. True isotropic resolution</td>
<td>Good</td>
</tr>
<tr>
<td>Temporal resolution</td>
<td>Good</td>
<td>Good</td>
</tr>
<tr>
<td>Dynamics on angiogram</td>
<td>Multiple dynamics possible, but not preferred in children due to radiation risk</td>
<td>Multiple dynamics routinely performed, with separation of right-sided, left-sided and venous structures</td>
</tr>
<tr>
<td>Flow</td>
<td>No flow quantification possible</td>
<td>Flow quantification possible, including stroke volume, Qp:Qs, regurgitant fraction, gradient across stenosis</td>
</tr>
<tr>
<td>Function</td>
<td>Quantitation of ventricular function possible, but less temporal resolution, along with increased radiation</td>
<td>Quantitation of biventricular function with excellent temporal resolution</td>
</tr>
<tr>
<td>Duration of study</td>
<td>Very short (less than 1 minute)</td>
<td>Long (30–60 minutes)</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Acute renal failure, anaphylaxis to iodinated contrast</td>
<td>Pacemakers, AICD</td>
</tr>
<tr>
<td>Compatibility with coils, stents and metallic prostheses</td>
<td>Compatible. Metal causes only minimal artifact. Best non-invasive means of evaluating stent patency</td>
<td>Stents and prostheses cause local loss of signal. Hence, stent patency cannot be reliably assessed. Steel coils can cause a large artifact, resulting in non-diagnostic study. Platinum coils cause less artifact</td>
</tr>
<tr>
<td>Health risks</td>
<td>Radiation</td>
<td>Overheating of the body</td>
</tr>
<tr>
<td>Ideal indications</td>
<td>Coronary stenosis imaging, anomalous coronaries, emergent studies like aortic dissection or occluded BT shunt, vessel wall evaluation, airway evaluation, need to avoid sedation</td>
<td>Conditions requiring serial studies, screening studies, or conditions requiring evaluation of flow, valvular and ventricular function, and chamber morphology</td>
</tr>
</tbody>
</table>

AICD, automatic implantable cardioverter defibrillator; BT shunt, Blalock–Taussig shunt; Qp:Qs, pulmonary:systemic blood flow.
when compared with contrast angiography, or even magnetic resonance angiography, is the ability to visualize the vessel wall. CT also provides better delineation of the airway, mediastinal abnormalities, and the pulmonary parenchyma. Other advantages of CT include a reduced need for sedation in young patients, a very short procedure time, and the widespread availability of CT scanners and trained personnel.

In situations where there is a need for serial evaluation, as in monitoring of aortic root dilatation in tetralogy of Fallot or after a Ross procedure, size of coronary aneurysms in Kawasaki disease, or aortic wall thickness in familial hypercholesterolemia, MRI may be a better choice than CT, because of the risk of cumulative radiation dose associated with the latter.

A comparison between CT and MRI in CHD is given in Table 14.4.

### Head ultrasound and other brain imaging modalities

The risk of neurodevelopmental impairment is the most significant concern following repair of CHD, especially in the vulnerable neonatal period. The presence of preoperative neurologic injury increases the risk of extension of the deficit postoperatively and in the long term. However, the most reliable imaging tool to use for neonates to detect brain injury remains controversial. Although head ultrasound (HUS) continues to be a routine tool in many pediatric cardiac centers, a recent report clearly showed that HUS was not indicated especially in asymptomatic patients. In a series of 167 near- or full-term infants scheduled for cardiac surgery, HUS had evidence of brain injury in 3% of patients compared with 26% on MRI. More importantly, 80% of the HUS findings were false positives [81]. Similar to other reports, abnormal preoperative brain MRI findings are seen in 25–40% of infants with CHD, and correlated with short- and long-term neurodevelopmental impairment. The most common abnormalities seen were white matter injuries, intraventricular hemorrhage, and stroke [82]. Thus, whether there are no symptoms or a suspicion of a preoperative injury, routine HUS is not the preferred screening tool, and brain MRI is a more reliable modality. It is important to state that the presence of clinically silent preoperative brain injury on MRI has low risk of progression and should not delay or preclude clinically indicated and urgent cardiac surgery [83].

### Preoperative preparation

#### Preoperative fasting

The American Society of Anesthesiologists published revised preoperative fasting guidelines in 2010 [84]. These guidelines are the same for children with CHD [85]. Preoperative fasting remains liberalized to allow oral hydration with clear fluids up to 2 hours prior to the surgical procedure. No increase in gastric volume or acidity has been shown in children with CHD with these liberalized guidelines [86]. Liberal oral hydration is particularly important in children who are cyanotic, polycythemic, those children with outflow tract obstruction, such as hypertrophic cardiomyopathy and aortic stenosis, bivacal pulmonary anastomosis, and shunt-dependent physiology. Children allowed clear liquids on the morning of the surgery were found to be less clinically dehydrated as measured by dry mucous membranes and delayed capillary refill [87]. Preoperative dehydration may be reduced by pre-admitting high-risk children, such as those mentioned earlier, and starting IV hydration until the procedure. If a surgical procedure is delayed, children should be allowed clear oral hydration through the delay. Additionally, liberal oral hydration reduces the risk of hypoglycemia in high-risk children, particularly infants less than 6 months of age who have impaired glycogenolysis and gluconeogenesis and immature glycogen stores. Finally, despite liberalization of clear oral hydration, nil per os (NPO) times should still be verified to reduce the risk of gastric aspiration.

### KEY POINTS: PREOPERATIVE IMAGING STUDIES

- Chest radiographs are essential preoperative information and play an important role in determining the physiology of CHD.
- Transthoracic echocardiography is the mainstay of preoperative diagnostic imaging but is less reliable with poorer windows as patients age and in the postoperative state.
- Cardiac catheterization is used less frequently for diagnosis, but is essential to determine pulmonary to systemic blood flow, PVR, and saturations and pressures in cardiac chambers and vessels in complex lesions.
- Cardiac MRI is a non-invasive modality that is excellent for extracardiac anatomy but requires sedation or anesthesia in young children.
- Cardiac CT is excellent for extracardiac anatomy and is a brief study that requires minimal to no sedation, but it does expose developing patients to ionizing radiation.
- The choice among cardiac catheterization, echocardiography, CT, or MRI for diagnostic anatomic information is complicated and deserves multidisciplinary discussion, including with the anesthesiologist.
Preoperative psychological preparation and premedication

The goal of premedication is to decrease preoperative anxiety, facilitate parental separation, improve cooperation at induction, and reduce sympathetic response at induction. Premedication should be integrated as part of the preoperative assessment. Premedication should not be the rescue solution to a lack of proper preoperative preparation and interaction with the child and family. Preoperative assessment begins with the psychological preparation of the child and the family by developing a rapport with the child and the family. Young children, children with high baseline anxiety, and those with previous negative interactions are at high risk for extreme preoperative anxiety [88]. Pharmacologic premedication is one aspect of the multimodal therapies, such as behavioral preparation programs, parental presence at induction, and distraction techniques. Many children have had multiple previous non-cardiac procedures, cardiac surgery, or cardiac catheterizations, and their concerns may be different from the child who has not had been previously anesthetized.

There are multiple benefits to premedication. It eases parental separation and facilitates induction by reducing the amount of inhalational or IV agent necessary for induction. Cyanotic CHD is not a contraindication to premedication. Premedication not only decreases oxygen consumption and increases oxygen saturation in cyanotic children but also achieves sedation and anxiolysis with minimal hemodynamic or respiratory effects. However, respiratory depression with impaired ventilation and oxygenation may occur with multimodal therapy or overdose. An anesthesiologist should be immediately available during and after premedication to monitor ventilation and oxygenation.

Numerous sedative-hypnotics have been used as premedications. Midazolam is the most commonly administered premedication and may be administered by different routes (intranasally 0.3 mg/kg, orally 0.5–1 mg/kg, rectally 0.5–1.0 mg/kg, IV 0.05 mg/kg). The oral route is the most well tolerated and easily administered. Although increasing doses of 0.75 and 1 mg/kg of oral midazolam are also efficacious, increased ataxia, diplopia, and dysphoric reactions were observed at these higher doses [89]. The nasal route is uncomfortable secondary to the burning sensation and bitter taste. The rectal route has largely been abandoned because the absorption and plasma concentrations are unpredictable. Reliable sedation and anxiolysis were achieved in more than 75% of children at 7.7 ± 2.4, 12.5 ± 4.9, and 16.3 ± 4.2 minutes after intranasal, oral, and rectal administration, respectively [90]. IV midazolam 0.05–0.2 mg/kg is an effective premedication with minimal hemodynamic and respiration effects in those children with an in situ IV access.

Intramuscular ketamine 2–5 mg/kg also provides rapid and effective premedication in 5–20 minutes, particularly in those children who are unwilling to accept an oral premedication, secondary to behavioral problems or cognitive issues, or who do not have IV access. Oral ketamine 2–10 mg/kg may also be combined with oral midazolam 0.5 mg/kg to decrease the incidence of adverse events with ketamine and shorten the onset time of anxiolyis. Intranasal sufentanil 2–4 μg/kg is also effective but used infrequently in children as it may precipitate chest wall rigidity. Most recently, intranasal dexmedetomidine 0.5–1 μg/kg has been used as a premedication although the onset of action is delayed at 45 minutes [91].

Infective endocarditis antibiotic prophylaxis

Infective endocarditis (IE) remains a significant risk for patients with CHD, with a cumulative incidence of 1.1–6/1,000 children, compared with 1.7–6.2/100,000 in the general population. In a large, population-based cohort study of the Quebec CHD Database from 1988 to 2010, the highest risk was with cyanotic lesions, endocardial cushion defects and left-sided obstructive lesions [92]. Invasive dental procedures, cardiac surgery within 6 months and age < 3 years also increased IE incidence and outcome. The AHA revised the indications for bacterial endocarditis prophylaxis in 2007 [93]. The AHA does not recommend prophylaxis for children undergoing routine gastrointestinal, urologic, and genitourinary procedures with no infected tissue involvement. The indications for bacterial endocarditis prophylaxis have been narrowed significantly compared with previous guidelines and are shown in Box 14.1 and the antibiotic regimens are listed in Box 14.2. Chapter 30 presents additional information about IE prophylaxis.

Box 14.1: Indications for infective endocarditis prophylaxis

- Prosthetic cardiac valve
- History of infective endocarditis
- Unrepaired cyanotic congenital heart defect, including palliative shunts and conduits
- Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure
- Repaired congenital heart defect with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibits endothelialization)
- Cardiac transplantation recipients with cardiac valvular disease

Sickle cell disease

The primary clinical manifestations of sickle cell disease are associated crises, including vaso-occlusive, pulmonary dysfunction (acute chest syndrome), aplastic; infection from splenic dysfunction; and chronic organ damage from
chronic sickling, including sickle cell nephropathy, cerebral vascular accidents, and pulmonary hypertension.

**Box 14.2: Treatment regimens for infective endocarditis**

**Standard general prophylaxis**

- **Ampicillin**
  - Adult dose: 2 g per os (PO)
  - Pediatric dose: 50 mg/kg PO; not to exceed 2 g/dose

- **Clindamycin**
  - Adult dose: 600 mg PO
  - Pediatric dose: 20 mg/kg PO; not to exceed 600 mg/dose

**Unable to take oral medication**

- **Ampicillin**
  - Adult dose: 2 g intravenous/intramuscular (IV/IM)
  - Pediatric dose: 50 mg/kg IV/IM; not to exceed 2 g/dose

**Allergic to penicillin**

- **Clindamycin**
  - Adult dose: 600 mg PO
  - Pediatric dose: 20 mg/kg PO; not to exceed 600 mg/dose

**Allergic to penicillin and unable to take oral medication**

- **Clindamycin**
  - Adult dose: 600 mg IV
  - Pediatric dose: 20 mg/kg IV; not to exceed 600 mg/dose

Source: Wilson et al. [93]. Adapted with permission of Lippincott, Williams & Wilkins.

There is a concern that CPB may cause sickling and complications such as hemolysis and vaso-occlusive crises from the combined effects of a stressful insult, cooling, and slow red blood cell transit time through the pump. Subsequently, preoperative exchange transfusion is often recommended. There are reports of intraoperative exchange transfusion with the CPB circuit to reduce the sickle cell load. The Preoperative Transfusion in Sickle Cell Disease Study Group randomized children between an aggressive preoperative exchange transfusion (lowering hemoglobin S to < 30%) and a less aggressive simple transfusion (raising hemoglobin to > 10 g/dL). Complications related to transfusion were twice as common in the exchange transfusion arm, with no difference in perioperative complications. The exact safe percentage of sickle cell hemoglobin for CPB had never been calculated, but a value of < 30%, as with other forms of surgery on these children, has been suggested. Chapter 7 presents additional information about sickle cell disease and CPB.

**KEY POINTS: PREOPERATIVE PREPARATION**

- Preoperative fasting guidelines are identical for CHD and non-CHD patients; however, CHD patients with systemic-to-pulmonary shunts, cyanosis, and left ventricular outflow tract lesions must not be allowed to become hypovolemic preoperatively.
- Standard premedications, including midazolam, ketamine, and dexmedetomidine, may be used safely in CHD patients, but they must be monitored closely for respiratory depression and desaturation.
- Infective endocarditis prophylaxis is an important consideration in CHD, and the patient’s cardiac condition and procedural indication must be assessed to avoid unnecessary antibiotic administration.

**Risk stratification**

There is an increased risk of perioperative cardiac arrest in children with CHD undergoing both cardiac and non-cardiac procedures. The Pediatric Perioperative Cardiac Arrest (POCA) registry reported that 34% of perioperative cardiac arrests over an 11-year period occurred in children with CHD. More than half (54%) of the cardiac arrests in these children were in the general operating rooms, compared with 26% in the cardiac operating rooms and 17% in the cardiac catheterization laboratory. The highest incidence of intraoperative cardiac arrest occurred in children with single-ventricle physiology, and arrests in children with severe aortic stenosis and cardiomyopathy were associated with the highest mortality rates. Three-quarters of the perioperative cardiac arrests in children with CHD were in children less than 2 years of age, and approximately 75% of the perioperative deaths in children with CHD occurred in children with severe aortic stenosis, cardiomyopathy, and single-ventricle physiology. Additional large databases have also confirmed an increased risk of perioperative cardiac arrest and mortality in children undergoing non-cardiac procedures. Although there are multiple published reports for the management of children with CHD, there is no established methodology to address the magnitude of incremental risk conferred by the degree of severity and compensation of the heart disease. The methods available for predicting risks in children with CHD, such as the Risk Adjustment for Congenital Heart Surgery (RACHS-1) score, the Basic Aristotle Complexity Score, and the Society of Thoracic Surgeons and the European Association for Cardiothoracic Surgery Mortality score (STS-EACTS score) are limited to children undergoing only cardiac surgery. These scores risk-stratify children on the complexity of the cardiac surgical procedure rather than the underlying pathophysiology and child’s degree of clinical compensation. RACHS-1 stratifies anatomic diversity into six categories based on age, type of surgery, and in-hospital mortality, using in-hospital mortality as the
outcome measured. Category 1 has the lowest in-hospital mortality and category 6 has the highest (Table 14.5). The RACHS-1 method was developed to adjust for baseline case mix differences for comparing discharge mortality, using a combination of judgment-based and empirical methodologies. The Basic Aristotle Complexity Score assigns a score to each operation, ranging from 1.5 to 15 (with 15 the most complex, based on the primary procedure of the operation). Each procedure is next assigned an index level, which is an integer range of 1 through 4, based on the initial basic score. The Aristotle basic score level provides a broad generalization of complexity by dividing surgical procedures from complexity levels. The fundamental principle of the Aristotle Complexity Score is to define the complexity as a constant for the challenge presented by a given surgical procedure. The complexity is the sum of three factors or indices: the potential for operative mortality, the potential for operative morbidity, and the technical difficulty of the operation. The Comprehensive Aristotle Complexity Score further discriminates from the basic score by incorporating two patient modifiers: procedure-dependent factors, including anatomical factors, associate procedures, and age at procedure; and procedure-independent factors, including general factors such as weight. Mortality is calculated on the basis of admission, but only the index operation is analyzed, with the index operation defined as the first operation of the admission that is of operation type “CPB” or “No CPB cardiovascular.” The numerator is the number of index operations performed during hospitalizations in which the children died before discharge, and the denominator is the number of index operations. The Aristotle Complexity Score classifies more operations, whereas the RACHS-1 discriminates better at the higher end of complexity. The primary objective of the Aristotle Complexity Score is to evaluate and compare surgical management and performance and not predict operative mortality for an individual patient. A recent abstract reported the perioperative complications of children with CHD undergoing non-cardiac procedures using the RACHS-1 score in one tertiary care pediatric cardiac center [111]. Unfortunately, this score is a surgical risk stratification score used to compare inter-institutional perioperative morbidity and mortality following cardiac surgery rather than risk-stratifying children for non-cardiac procedures. Chapter 3 presents additional discussion about risk stratification methods for congenital cardiac surgery.

Preoperative risk assessment of adults with acquired heart disease has helped to identify patients at risk for perioperative complications following non-cardiac surgery. Several risk scoring systems have been developed and validated to identify high-risk adult patients undergoing cardiac and non-cardiac surgery, including those by the AHA and the American College of Cardiology (ACC), the EUROSCORE, and the Cleveland Clinic score [112,113]. The AHA/ACC system risk stratifies clinical predictors of increased preoperative risk into major, intermediate, and minor predictors. These clinical predictors place adults undergoing non-cardiac surgery into high (>5%), intermediate (1–5%), and low (<1%) risk for perioperative complications. Risk adjustment for adult heart disease is potentially easier than pediatric heart disease as there is less variation in anatomy and pathophysiology.

Risk stratification of children with CHD is challenging due to the smaller number of patients and the higher number of procedure types. Six primary requirements are needed to facilitate meaningful multi-institutional analysis of outcomes: common language; mechanism of data collection; mechanism for evaluating case complexity; mechanism to ensure and verify completeness and accuracy of the data; collaboration between medical and surgical subspecialties; and mechanism to obtain

### Table 14.5 Risk Adjustment for Congenital Heart Surgery Score (RACHS-1)

<table>
<thead>
<tr>
<th>Category</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PDA &gt;30 d</td>
</tr>
<tr>
<td></td>
<td>Coarctation &gt;30 d</td>
</tr>
<tr>
<td></td>
<td>ASD</td>
</tr>
<tr>
<td>2</td>
<td>VSD</td>
</tr>
<tr>
<td></td>
<td>TOF</td>
</tr>
<tr>
<td></td>
<td>Vascular ring</td>
</tr>
<tr>
<td></td>
<td>Coarctation &lt;30 d</td>
</tr>
<tr>
<td></td>
<td>AP Window</td>
</tr>
<tr>
<td>3</td>
<td>ASO</td>
</tr>
<tr>
<td></td>
<td>TOF/PA</td>
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<tr>
<td></td>
<td>Ross</td>
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<td></td>
<td>ALCAPA</td>
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<tr>
<td></td>
<td>DORV repair</td>
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<tr>
<td></td>
<td>Coarctation/VSD</td>
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<tr>
<td></td>
<td>BTS</td>
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<tr>
<td></td>
<td>CAVC</td>
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<td>PAB</td>
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<td>Double switch</td>
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<td>Hypoplastic arch repair</td>
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<tr>
<td></td>
<td>Unifocalization</td>
</tr>
<tr>
<td></td>
<td>Rastelli</td>
</tr>
<tr>
<td></td>
<td>ASO/VSD</td>
</tr>
<tr>
<td></td>
<td>Konno</td>
</tr>
<tr>
<td>5</td>
<td>TV repositioning in Ebsteins anomaly &lt;30 d</td>
</tr>
<tr>
<td></td>
<td>TruncusIAA</td>
</tr>
<tr>
<td>6</td>
<td>Norwood Procedure</td>
</tr>
<tr>
<td></td>
<td>DKs</td>
</tr>
</tbody>
</table>

Source: Jenkins et al. [108]. Reproduced with permission of Elsevier. PDA, patent ductus arteriosus; ASD, atrial septal defect; VSD, ventricular septal defect; TOF, tetralogy of Fallot; AP, aortopulmonary; ASO, arterial switch operation; TOF/PA, tetralogy of Fallot with pulmonary atresia; ALCAPA, anomalous left coronary artery from the pulmonary artery; DORV, double outlet right ventricle; BTS, Blalock-Taussig shunt; CAVC, complete atroventricular canal; PAB, pulmonary artery banding; TV, tricuspid valve; IAA, interrupted aortic arch; DKs, Damus-Kaye-Stansel procedure.
Table 14.6  Sample risk stratification score for children with congenital heart disease

<table>
<thead>
<tr>
<th>CHD</th>
<th>0</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repaired CHD</td>
<td>Simple</td>
<td>Moderate (ASD/PS)</td>
<td>Complex (TOF/d-TGA)</td>
</tr>
<tr>
<td>Obstruction (right- or left-sided)</td>
<td>None</td>
<td>Repaired with residual</td>
<td>Palliated or unrepaired</td>
</tr>
<tr>
<td>Ventricle</td>
<td>2</td>
<td>1</td>
<td>1 (or 2)</td>
</tr>
<tr>
<td>Systemic ventricular dysfunction</td>
<td>Mild</td>
<td>LV systemic</td>
<td>RV systemic</td>
</tr>
<tr>
<td>PVR</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
</tr>
<tr>
<td>PVR</td>
<td>2 WU</td>
<td>Moderate</td>
<td>Severe</td>
</tr>
<tr>
<td>SpO$_2$</td>
<td>&gt;90%</td>
<td>PAP &lt; 1/2 systemic</td>
<td>&gt;4 WU</td>
</tr>
<tr>
<td>HCT%</td>
<td>30–45%</td>
<td>25–30% and 45–65%</td>
<td>PAP ≥ systemic</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>Rare</td>
<td>Atrial</td>
<td>&lt;75%</td>
</tr>
<tr>
<td>Drugs (anticoagulants, anti-arrhythmics, diuretics, inotropes, others)</td>
<td>Not requiring therapy</td>
<td>Ventricular</td>
<td>&lt;25% or &gt; 65%</td>
</tr>
<tr>
<td>Surgical Severity</td>
<td>Minor (non-invasive or diagnostic)</td>
<td>Intermediate (peripheral)</td>
<td>Major (intracavitary)</td>
</tr>
<tr>
<td>Surgical urgency</td>
<td>Elective</td>
<td>Urgent (&lt; 24 hours)</td>
<td>Emergent</td>
</tr>
</tbody>
</table>

ASD, atrial septal defect; PS, pulmonary stenosis; TOF, tetralogy of Fallot; LV, left ventricle; RV, right ventricle; SBF, systemic blood flow; HLHS, hypoplastic left heart syndrome; IAA, interrupted aortic arch; AS, aortic stenosis; VSD, ventricular septal defect; d-TGA, dextro-transposition of the great arteries; PVR, pulmonary vascular resistance; SpO$_2$, pulse oximeter saturation; HCT, hematocrit; WU, Wood units; PAP, pulmonary artery pressure; ICD, implantable cardioverter defibrillator.

Longitudinal follow-up data. The development of a risk stratification scoring system for children with CHD undergoing non-cardiac procedures may not only help identify children at increased risk for perioperative complications, but also aid in resource utilization. For example, it can be used to determine whether the procedure can be performed safely in an outpatient surgery center or whether it needs to be performed in a tertiary center with cardiothoracic surgery and intensive care back-up based on the child’s score. Does a poorly compensated child with a high-risk score need to see their cardiologist to optimize medical management prior to their elective procedure? Does that child need additional diagnostic tests or cardiac interventions prior to the procedure? Adult literature on preoperative conditioning has greatly improved outcomes for adults undergoing cardiac and non-cardiac surgery. Simple maneuvers, such as smoking cessation, starting beta-blockers, statins, aspirin, or an exercise program, can mitigate risk. A scoring system may also be valuable for children with CHD. Can we take certain steps to change a child with a high-risk score to a lower score?

The score can help determine if it is appropriate for the anesthetic to be administered by an anesthesiologist who usually takes care of adults, a pediatric anesthesiologist, or even someone whose practice is limited to pediatric cardiac cases. The score can therefore provide crucial information to the child, the child’s family, and the entire perioperative team, including the anesthesiologist, the surgeon, the cardiologist, and the pediatrician.

**KEY POINTS: RISK STRATIFICATION**

- CHD patients are significantly more likely to suffer cardiac arrest during anesthesia than patients without heart disease; over 50% of arrests occur outside the cardiac operating room or catheterization laboratory.
- There are several risk stratification methods for hospital mortality after cardiac surgery, but to date no validated method to stratify pre-anesthetic risk for death or major complication taking into account CHD has been published.
- A proposed risk assessment strategy for CHD takes into account a number of anatomical and physiological components of the CHD, as well as the complexity and urgency of surgery.

Risk factors in a scoring system may include the type, complexity, and stage of repair of the heart defect; the number of functioning ventricles; the side of the systemic ventricle; the presence and degree of cardiac decompensation; the degree of pulmonary vascular disease; the degree of right- or left-sided obstructive disease; the extent of cyanosis; the level of polycythemia; the type of arrhythmias; the number and type of medications; the type of surgery (per the RACHS-1 or Basic Aristotle Complexity Score for cardiac surgery and minor, intermediate, or
A sample scoring system is listed in Table 14.6. Although not validated, this scoring card has the advantages of simple application and the ability to quickly identify children with decompensated or high-risk CHD, and it incorporates various aspects of the child’s condition and the planned procedure or intervention requiring anesthesia.

**Selected references**

A full reference list for this chapter is available at:

http://www.wiley.com/go/andropoulos/congenitalheart


CHAPTER 15

Approach to the Fetus, Premature, and Full-Term Neonate

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Introduction

The advances in pediatric cardiology and cardiac surgery over the past 30 years have resulted in a substantial decrease in morbidity and mortality associated with congenital heart disease (CHD). Most congenital heart lesions are now amenable to either anatomical or physiological repair early in infancy. Opinion regarding the optimal timing of corrective surgery for infants with symptomatic CHD regardless of age or weight has undergone radical changes over the past several decades. Rather than the previous strategy of initial palliation followed by correction in early childhood, the current approach favors complete repair within days to weeks of birth, if feasible. Advances in diagnostic and interventional cardiology, the evolution of surgical techniques and management of cardiopulmonary bypass (CPB) as well as refinements in postoperative care have all contributed to the successful strategy of early corrective two-ventricle repair. Most recently this approach has also been extended to include premature and low-birth-weight neonates (LBWNs). However, the low mortality achieved with two-ventricle repairs has not been the experience in LBWNs undergoing palliation for single-ventricle defects, such as hypoplastic left heart syndrome (HLHS).

Cardiac surgery in the premature and very low-birth-weight (LBW) infants presents additional challenges for the anesthesiologist. As for any pediatric cardiac procedure, a thorough understanding of the pathophysiology of various defects, the planned surgical procedure, and anticipation of specific postoperative problems is essential. There are further considerations, however, when providing anesthesia to the premature and LBW neonate: immaturity of the airway, lungs, cardiovascular system, liver, kidney, and central nervous system makes these infants more susceptible not only to surgical but also to anesthetic complications. Finally, as the limits for managing CHD continue to be extended, fetal cardiac interventions (FCIs) emerge as the next challenging frontier.

This chapter will describe general principles relevant to anesthesia for the newborn, including the premature and the very LBW neonate with CHD. The impact of prematurity, the outcome of cardiac surgery in the premature and full-term neonate, and new directions with FCIs will be discussed.

Approach to treatment in the neonate

Early palliation

In the early days of cardiac surgery for neonates, particularly those with LBW born prematurely, initial palliation or medical management of congenital cardiac defects was preferred. With technical limitations for various surgical
### Key Points: Early Palliation

- This was the classical approach in the early days of pediatric cardiac surgery due to technical limitations.
- Typical procedures are pulmonary artery banding or systemic-to-pulmonary artery shunt.
- The goal is adequate control of pulmonary blood flow to allow for growth without pulmonary overcirculation, cyanosis, impaired systemic perfusion, or volume load on the ventricle.
- It is often technically challenging and associated with many potential early and late complications.

### Key Points: Systemic-to-Pulmonary Artery Shunt (e.g., Modified BT Shunt)

- The appropriate size is difficult to determine.
- If the shunt too large, there is a risk of pulmonary overcirculation, congestive heart failure and development of PVOD.
- If the shunt is too small, the risk is of inadequate pulmonary blood flow and cyanosis, shunt thrombosis, and early surgery.
- Late complications are distortion and/or asymmetrical growth of pulmonary arteries, and PVOD.

### Table 15.1 Complications of palliative surgery

<table>
<thead>
<tr>
<th></th>
<th>Early complications</th>
<th>Late complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic-to-pulmonary artery shunt</td>
<td>Excessive pulmonary blood flow Heart failure</td>
<td>Distortion of pulmonary arteries</td>
</tr>
<tr>
<td></td>
<td>Inadequate pulmonary blood flow Cyanosis</td>
<td>Asymmetrical growth of the pulmonary arteries Pulmonary vascular occlusive disease</td>
</tr>
<tr>
<td></td>
<td>Shunt obstruction: Thrombus Mechanical</td>
<td></td>
</tr>
<tr>
<td>Pulmonary artery banding</td>
<td>Band too loose: excessive pulmonary blood flow</td>
<td>Complications at band site: Distortion and residual stenosis after repair Aneurysm</td>
</tr>
<tr>
<td></td>
<td>Band too tight: inadequate pulmonary blood flow</td>
<td>Complications proximal to band site: Right ventricular hypertrophy Subaortic stenosis Pulmonary valve stenosis</td>
</tr>
</tbody>
</table>

The goal of palliative procedures is to control pulmonary blood flow sufficiently to allow for growth, but without excessive blood flow to the pulmonary circulation and impaired systemic perfusion and volume overload to the systemic ventricle. Nevertheless, palliation with a pulmonary artery (PA) band or a modified systemic-to-pulmonary artery shunt, such as a modified Blalock-Taussig (BT) shunt, can be technically demanding procedures in neonates and tend to be even more problematic in LBWNs (see Table 15.1). For example, the appropriate size of a systemic-to-pulmonary shunt can be very difficult to determine, and the geometry of the shunt is critical. A relatively large shunt may lead to excessive pulmonary blood flow, congestive heart failure (CHF) and possible pulmonary vascular obstructive disease (PVOD). Conversely, a small shunt can result in inadequate pulmonary blood flow, lower arterial oxygen saturation \( \text{SaO}_2 \), possible shunt thrombosis and distortion or stenosis of pulmonary arteries, making further repair all the more challenging. Assuming a normal cardiac output and hematocrit, absence of pulmonary venous desaturation and unrestricted mixing of systemic and pulmonary venous return in the atrium, an ideal \( \text{SaO}_2 \) between 80% and 85% indicates a relatively balanced circulation with a pulmonary to systemic blood flow ratio \( \text{Qp:Qs} \) close to 1:1. In our experience, a modified BT shunt of 3.5 mm is the optimal size to use in a term neonate > 3.0 kg. If a 3.0 mm shunt is used, the risk for sudden thrombosis and acute obstruction in the early postoperative period is increased, even in LBWNs. Early introduction of anticoagulation with low-dose heparin 10–20 units/kg/hour is important.
once hemostasis has been secured after surgery. A further problem of a small shunt is the likelihood of outgrowing the shunt size causing progressive cyanosis and requiring earlier surgical intervention. On the other hand, if a larger shunt size (i.e. > 4.0 mm) is used in a newborn, the excessive pulmonary blood flow may compromise systemic perfusion, cause ventricular volume overload, heart failure, and prolonged postoperative recovery.

Banding of the pulmonary artery to reduce pulmonary blood flow can also be a challenging palliative procedure. If the band is too tight, severe cyanosis may occur, and if the band is too loose, the increase in pulmonary blood flow will contribute to CHF and possible PVOD. Distortion of the pulmonary artery secondary to migration of the band may contribute to both proximal and distal artery stenoses and complicate later repair, but can also lead to right ventricular hypertrophy, subaortic stenosis and pulmonary valve stenosis, depending on the relationship of the great arteries to the ventricular outflow tract. Determining the correct size of a band at the time of band placement must be closely observed. Ideally, the banded PA will result in an increase in systemic systolic blood pressure by 20%, and, depending on the underlying pathology, a fall in SaO₂ to around 85% breathing room air. The pressure gradient across the band can also be directly measured; usually a pressure difference of approximately 50% proximal to distal across the band is sufficient. Monitoring hemodynamic changes at the time of band placement is essential, and anesthetic techniques that could decrease ventricular function or cardiac output are best avoided. Therefore, an opioid technique is most often necessary, and extubation should be delayed until the hemodynamic effect of the band is determined as the patient emerges from anesthesia and starts to wean from mechanical ventilation.

The case for early complete repair
As noted previously, whenever possible, early two-ventricle repair of congenital cardiac defects is the preferred approach in the modern era. Avoiding the long-term consequences of excessive volume and pressure overload on the ventricles and pulmonary vasculature as well as the potential detrimental effect of chronic hypoxia, early repair allows for more normal growth and development.

The considerable advances in cardiac surgery and CPB techniques have contributed to a dramatic reduction in mortality following cardiac surgery in newborns [1–3], but these patients nevertheless remain at risk for significant end-organ impairment, particularly neurological injury [4]. Medical management alone, with the goal of controlling pulmonary blood flow and volume overload on an immature myocardium, is often extremely difficult and unsuccessful [5].

Long-term effects associated with pulmonary overcirculation, chronic volume, and/or pressure load on the ventricles and cyanosis may substantially alter growth and development and lead to myocardial and pulmonary injury, which will influence the outcome of subsequent repairs [4]. In most newborns with a large left-to-right shunt, the imbalance between pulmonary and systemic blood flow will increase as pulmonary vascular resistance (PVR) falls in the first few weeks of life and the physiologic nadir in hematocrit is reached. The clinical manifestations of an infant with CHF are shown in Box 15.1. Tachypnea and the additional work of breathing, secondary to an increase in pulmonary blood flow and total lung water, raise the metabolic demand and the percentage of the total cardiac output directed toward respiratory muscle work (most notably the diaphragm). This essentially diverts cardiac output from other metabolically active functions, particularly from the splanchnic circulation and absorption of food. The abnormal circulatory physiology is unable to meet metabolic needs; and patients fail to thrive.

**Box 15.1:** Symptoms and signs of congestive heart failure in neonates and infants

**Low cardiac output**
- Tachycardia
- Poor extremity perfusion
- Cardiomegaly
- Hepatomegaly
- Gallop rhythm

**Increased respiratory work**
- Tachypnea
- Grunting
- Flaring of ala nasi
- Chest wall retraction

**Increased metabolic work**
- Failure to thrive
- Poor weight gain

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**KEY POINTS: BANDING OF MAIN PULMONARY ARTERY**

- Difficult intraoperative adjustment with constant monitoring of hemodynamic changes, requires stable anesthetic technique with minimal negative effects on ventricular function.
- The goals are an increase in systemic blood pressure by 20%, a decrease in SaO₂ to 85% on room air, and a pressure gradient of 50%. If the shunt is too small, there is a risk of inadequate pulmonary blood flow and cyanosis, and shunt thrombosis.
- Late complications are migration of the band, distortion, stenosis or aneurysms of pulmonary arteries, right ventricular hypertrophy, subaortic stenosis, and pulmonary valve stenosis.
While it is preferable to correct congenital cardiac defects early in the full-term newborn to promote normal growth and development, this may be difficult to achieve in the premature and very LBW neonate [6–12]. The causes are multifactorial, and include technical issues related to small cardiac structures and cannulation requirements for CPB, the immaturity of organ systems (especially the lungs, myocardium, and germinal matrix in the brain), increased risk of bleeding from coagulopathy after CPB, and an immature stress response that may increase the risk for infection and promote a catabolic state in a newborn with limited nutritional reserves. All these factors contribute directly to the increased mortality risk as well as longer duration of mechanical ventilation, intensive care, and hospital stay for the premature and LBW newborn undergoing cardiac surgery. Recently, several single-center reports have suggested some improvements in outcome with individualized management strategies for these high-risk neonates [13–15].

**Outcome**

Although the risk for early mortality in neonates undergoing cardiac surgery and CPB may be increased, randomized and prospective studies comparing the morbidity that may occur in neonates with critical lesions who are treated medically in hopes of weight gain with surgical morbidity and mortality have not been performed. Such has been the nature for many of the advances in CHD management.

For example, infants with an increased pulmonary blood flow who undergo delayed surgical intervention often fail to thrive and are at risk of recurrent respiratory infections. Their work of breathing and energy expenditure is significantly increased, and cardiomegaly with hyperinflated lung fields is evident on chest radiograph. Cardiac surgery and CPB may be delayed because of concerns for intercurrent infection and the risk of exacerbation or reactivation of inflammatory lung processes, which in turn may cause intrapulmonary shunting and severe hypoxemia, pulmonary hypertension, and prolonged mechanical ventilation. The early repair or palliation of defects to limit pulmonary overcirculation and volume load on the systemic ventricle will often avoid these complications.

The management of neonates in the immediate postoperative period after a two-ventricle repair can be a challenge, but with the substantially improved outcomes recently, mortality alone is no longer a reliable index against which to measure or compare new or alternative treatments in this group of patients. The focus should rather shift to long-term quality of life, ongoing need for re-interventions, and hospital admissions. The situation is different for palliative procedures in patients with complex single-ventricle defects, even though there has been a steady improvement in survival and longer-term outcomes in recent years [16].

**Limited physiologic reserve**

Care of the critically ill neonate requires an appreciation of the special structural and functional features of immature organs. The neonate appears to respond more quickly and extremely to physiologically stressful circumstances; this may be expressed in terms of rapid changes in, for example, pH, lactic acid, glucose, and temperature [17].

The physiology of the preterm and full-term neonate is characterized by a high metabolic rate and oxygen demand (two- to threefold increase compared with adults), which may be compromised at times of stress because of limited cardiac and respiratory reserve. The myocardium in the neonate is immature: contractile tissue constitutes only 30% of the myocardial mass, compared with 60% in mature myocardium. In addition, neonates have a lower velocity of shortening, a diminished length–tension relationship, and a reduced ability to respond to afterload stress [18,19]. Because the compliance of the myocardium is reduced, the stroke volume is relatively fixed, cardiac output is heart rate-dependent, and the Frank–Starling relationship is functional only within a narrow range of left ventricular end-diastolic pressure compared with the mature myocardium. The cytoplasmic reticulum and T-tubular system are underdeveloped and the neonatal heart is dependent on the trans-sarcolemmal flux of extracellular calcium both to initiate and to sustain contraction. It is important to note that much of this information is derived from animal data. It is not known to what extent prematurity causes an additional detriment in functional myocardial reserve. See Chapter 5 for further discussion of developmental physiology of the myocardium.

Cardiorespiratory interactions are important in neonates and infants. In simple terms, ventricular interdependence refers to the fact that a relative increase in ventricular end-diastolic volume and pressure causes a shift of the ventricular septum and diminishes the diastolic compliance of the opposing ventricle [20]. This effect is particularly prominent in the immature myocardium. Therefore, a volume load from an intracardiac shunt or valve regurgitation, and a pressure load from ventricular outflow obstruction or increased vascular resistance, may lead to biventricular dysfunction. For example, in neonates with tetralogy of Fallot and severe outflow obstruction, hypertrophy of the ventricular septum may contribute to
diastolic dysfunction of the left ventricle and an increase in end-diastolic pressure. This does not improve immediately after repair in the neonate, as it takes some time for the myocardium to remodel. Therefore an elevated left atrial pressure is not an unexpected finding after neonatal tetralogy repair. A persistent volume load to the left ventricle following surgery, such as from a residual ventricular septal defect (VSD), may further exacerbate this situation.

The mechanical disadvantage of an increased chest wall compliance and reliance on the diaphragm as the main muscle of respiration limits ventilatory capacity in the neonate. The diaphragm and intercostal muscles have fewer type I muscle fibers (i.e., slow-contracting, high-oxidative fibers for sustained activity) and this contributes to early fatigue when the work of breathing is increased. In the newborn, only 25% of fibers in the dia phragm are type I, reaching a mature proportion of 55% by 8–9 months of age [21,22]. Diaphragmatic function may be significantly compromised by raised intra-abdominal pressure, such as from gastric distension, hepatic congestion, and ascites.

The tidal volume of full-term neonates is between 6 and 8 mL/kg and, because of the above mechanical limitations, minute ventilation is dependent on respiratory rate. The resting respiratory rate of the newborn infant is between 30 and 40 breaths/min, which provides the optimal alveolar ventilation to overcome the work of breathing and match the compliance and resistance of the respiratory system. When the work of breathing increases, such as with parenchymal lung disease, airway obstruction, cardiac failure, or increased pulmonary blood flow, a larger proportion of total energy expenditure is required to maintain adequate ventilation. Infants therefore fatigue readily and fail to thrive.

The neonate has a reduced functional residual capacity (FRC) secondary to increased chest wall compliance (FRC being determined by the balance between chest wall and lung compliance). Closing capacity is also increased in newborns, with airway closure occurring during normal tidal ventilation [23]. Oxygen reserve is therefore reduced, and in conjunction with the increased basal metabolic rate and oxygen consumption that is two to three times adult levels, neonates and infants are at risk for hypoxemia. However, atelectasis and hypoxemia do not occur in the healthy neonate because FRC is maintained by dynamic factors including tachypnea, breath stacking (early inspiration, expiratory breaking (expiratory flow interrupted before zero flow occurs) and from laryngeal breaking (auto positive end-expiratory pressure).

Drug pharmacodynamics and kinetics may be different in the newborn because of immature hepatic and renal function. In addition to altered drug metabolism, protein binding and clearance, the drug volume of distribution is affected by the increase in total body water of the neonate compared with the older patient. The propensity of the neonatal capillary system to leak fluid out of the intravascular space [24] is especially pronounced in the neonatal lung, in which the pulmonary vascular bed is almost fully recruited at rest, and increases in lymphatic flow required to handle elevated mean capillary pressures (due to augmented pulmonary blood flow) are limited [25].

The glomerular filtration rate is generally low at birth but normalizes over the first few months of life. Urinary sodium excretion increases slowly during the first 2 years of life, and the inability of immature kidneys to concentrate urine and to excrete acute water and sodium loads makes fluid management in neonates, and especially preterm infants, difficult. Urinary acidification capability is limited in neonates and the bicarbonate threshold is reduced. Thus premature infants have decreased serum bicarbonate levels and lower serum pH (a non-anion gap acidosis). Neonates tolerate fluid restriction poorly, so fasting should be kept to a minimum and intravenous (IV) fluid started early; however, excessive fluid administration (as after CPB) is also poorly tolerated. In order to induce diuresis in neonates, larger doses of furosemide compared with adults are needed. The dosing of drugs that mainly depend on renal excretion will have to be reduced and, if possible, the plasma concentration should be closely assessed in order to avoid accumulation and side-effects.

In order to meet the metabolic demand, the caloric requirement for neonates and especially preterm neonates is high (100–150 kcal/kg/24 hours). Supplying adequate nutrition can be a difficult task, especially if the total amount of fluid, administered either parenterally or enteraly, has to be restricted, as is the case in premature neonates with CHD. Hyperosmolar feedings have been associated with an increased risk of necrotizing enterocolitis (NEC) in the preterm neonate or in the full-term neonate who has decreased splanchnic blood flow of any cause (e.g. left-sided obstructive lesions) [26].

**KEY POINTS: LIMITED PHYSIOLOGIC RESERVE**

- The immature myocardium has less contractile elements, poor compliance, fixed stroke volume, heart rate-dependent cardiac output, and immature T-tubular system.
- There is also ventricular interdependence.
- Limited ventilatory capacity results in increased chest wall compliance, early respiratory muscle fatigue, and increased closing capacity.
- Immature hepatic and renal function leads to altered drug pharmacokinetics and pharmacodynamics.
- There is high metabolic demand (100–150 kcal/kg/24 hour) and oxygen demand (6–8 mL/kg/min).

**Systemic inflammatory response to CPB**

It is well recognized that the exposure of blood elements to the non-endothelial surfaces of the CPB circuit, along
with ischemic–reperfusion injury, induces a systemic inflammatory response syndrome (SIRS), i.e. activation of numerous signaling cascades including complement, fibrinolytic, proinflammatory cytokine and oxygen free radical pathways. These effects are magnified in neonates due to the fairly large bypass circuit surface area and priming volume relative to patient blood volume.

The inflammatory response and its clinical manifestation are even more pronounced in very LBW and premature newborns, in part due to the immaturity of the responding systems, low receptor density, and low vascular tone. The clinical consequences include increased interstitial fluid, generalized capillary leak, and potential multi-organ dysfunction. Total lung water is increased with an associated decrease in lung compliance and increase in alveolar-to-arterial (A–a)O_2 gradient. Myocardial edema leads to impaired ventricular systolic and diastolic function. A secondary fall in cardiac output by 20–30% is common in neonates in the first 6–12 hours following surgery, contributing to decreased renal function and oliguria [27]. Sternal closure may need to be delayed due to mediastinal edema and associated cardiorespiratory compromise when closure is attempted. Ascites, hepatic congestion, and bowel edema may affect mechanical ventilation, cause a prolonged ileus, and delay feeding. A coagulopathy post-CPB may contribute to poor hemostasis and ongoing blood loss.

In recent years, numerous strategies have evolved to limit the effect of the endothelial injury resulting from SIRS. Understanding triggers, timing, and pattern of the complex cascades related to SIRS is essential to modify or attenuate this response. A variety of anti-inflammatory treatment modalities have been studied, including leukocyte depletion, neutrophil adhesion blockade, and heparin coating of the CPB circuit to reduce compliment and leukocyte activation. To date, no single treatment has been shown to attenuate the endothelial reaction and clinical response following CPB in neonates and infants, which highlights the multifactorial nature of the inflammatory response.

The most important strategy remains limiting both the time spent on bypass and the use of deep hypothermic circulatory arrest (DHCA). This is clearly dependent, however, upon surgical expertise, experience, and patient size. For the LBWN, DHCA is often still necessary for complete surgical repair. Attenuation of the stress response with deep anesthesia and hypothermia, the use of antioxidants such as mannitol, perioperative treatment with anti-inflammatory agents such as steroids, adjustments in prime composition to maintain hematocrit and oncocic pressures, and finally ultrafiltration during rewarming or immediately after bypass are all attempts to further limit the clinical consequences of the inflammatory response.

In addition to activation of stress hormones during CPB, triiodothyronine (T_3) levels have been shown to be low after CPB, and may remain low for up to 48 hours after surgery, particularly if a sick euthyroid state develops and there is decreased conversion of thyroxine to the active T_3 in peripheral tissues [28]. An increase in glucagon levels, insulin resistance, and steroid administration may contribute to significant hyperglycemia following bypass in neonates. Persistent hyperglycemia may contribute to adverse outcomes and risk for health care-acquired infections, but has not been associated with long-term neurologic injury [29]. The use of insulin to achieve tight glycemic control after bypass must be undertaken with caution, and frequent measurement of glucose levels is essential because of the risk of unintended hypoglycemia, which will cause neurologic injury [30]. Hemofiltration has become a technique commonly used to hemoconcentrate and possibly remove inflammatory mediators (e.g. complement, endotoxin, and cytokines) during or after CPB [31–35]. Hemofiltration techniques include “modified ultrafiltration,” whereby the patient’s blood volume is filtered after completion of bypass, “conventional hemofiltration,” whereby both the patient and circuit are filtered during rewarming on bypass, and “zero-balance ultrafiltration,” in which high-volume ultrafiltration essentially washes the patient and circuit blood volumes during the rewarming process [36]. High flow rates during modified ultrafiltration have been shown to transiently decrease the cerebral circulation in young infants compared with lower blood flow rates; this could be important in newborns after CPB who may have altered cerebral autoregulation [37].

Early clinical experience suggested improved systolic and diastolic pressures during filtration, as well as improved pulmonary function with reduction in PVR and total lung water [31,32]. While modified ultrafiltration post-bypass has been shown to improve early hemodynamic and pulmonary function, the initial increase in pulmonary compliance may not be sustained beyond the immediate post-ultrafiltration period [38]. These techniques are useful to hemoconcentrate and remove total body water, but they do not prevent the inflammatory response. And even if the SIRS is somewhat modified, the response is nevertheless idiosyncratic; despite all the above maneuvers, some neonates and infants will still manifest significant clinical signs of the SIRS and delayed postoperative recovery [38]. The development of drugs that will prevent the adhesion molecule/endothelial interaction, which is pivotal in the inflammatory response, continues to be pursued in both laboratory and clinical studies.

Peritoneal dialysis has been recommended as a means to treat total body fluid overload, particularly during low output states following cardiac surgery. Recent studies have reported successful treatment of fluid overload with continuous peritoneal dialysis, without significant morbidity and hemodynamic effects [39,40]. In addition to decompressing the abdomen, which may in turn improve respiratory mechanics and requirements for mechanical ventilation, peritoneal dialysis also assists with postoperative fluid balance and may have the potential benefit of removing proinflammatory cytokines [41].
Neurologic injury

Deep hypothermia (<18°C) with low-flow CPB or circulatory arrest may be necessary in selected neonates undergoing cardiac surgery either because of size limitations for cannulation and/or to facilitate the surgical procedure. In this situation, optimal myocardial and neurologic protection is highly dependent on the management of CPB.

In many centers, the practice has shifted away from the use of DHCA if the repair can be satisfactorily accomplished with low-flow techniques [42,43], or alternative cannulation and cerebral perfusion strategies that allow higher-flow bypass at moderate hypothermia. These alternative techniques are still being modified and evaluated [44,45]. While there may be no optimal “safe” duration of DHCA, the accepted limit has been reduced over recent years from approximately 60 minutes to a range of 30 minutes at temperatures < 20°C [3,43]. With improvements in neurologic protection over recent years, the incidence of overt injury, i.e. postoperative seizures, has declined substantially. While long-term neurodevelopmental outcome after DHCA in children is still being clarified, this has nevertheless become an important outcome variable when evaluating neurologic protection strategies [44,46–52].

Neurologic injury is an inherent risk for any patient undergoing cardiac surgery and CPB. Early in the development of bypass techniques, postoperative seizures were a relatively common occurrence. They were generally self-limiting and not associated with longer-term seizure activity. However, it is now clear that seizures are a manifestation of neurologic injury, consistent with the release of excitatory neurotransmitters which produce neuronal injury by N-methyl-d-aspartate (NMDA) receptor-gated calcium channels [53]. Adverse neurologic outcomes are multifactorial after bypass and may be secondary to the duration of CPB [54,55], rate and depth of cooling [56–58], perfusion flow rate [59], duration of circulatory arrest, pH management on bypass [1,53], hematocrit [2,5,6,1,61], and embolic events. Strategies to optimize cerebral protection during deep hypothermic bypass, with or without circulatory arrest, include a longer duration of cooling (>20 minutes), the use of pH-stat strategy of blood gas management during cooling (i.e. addition CO₂ to the oxygenator), and maintenance of a higher hematocrit (>25%) [45,49,62]. A recent randomized study of hematocrit of 25% vs. 35% showed no major benefits or risks overall among infants undergoing two-ventricle repair. It is important to note that developmental outcomes at age 1 year in both randomized groups were below those in the normal population [2], and this finding is consistent with the inherent risk of neurologic injury in all neonates undergoing CPB. Brain magnetic resonance imaging (MRI) data performed both before and after newborn cardiac surgery and hypothermic bypass demonstrates a disturbing incidence of white matter injury and the development of periventricular leukomalacia [63–71]. While the longer-term impact of these injuries is yet to be fully determined, the risk of brain injury in newborns is clear and supports the use of routine intraoperative neurologic monitoring with monitors such as near-infrared spectroscopy, transcranial Doppler assessment of cerebral blood flow velocity, and continuous EEG [49,50,72,73].
Stress response

In general terms, the “stress response” is a systemic reaction to injury, with hemodynamic, endocrinologic, and immunologic effects (Box 15.2). Stress and adverse postoperative outcome have been closely linked in critically ill newborns and infants. This is not surprising given their precarious balance of limited metabolic reserve and increased resting energy demand. Metabolic derangements, such as altered glucose homeostasis, acidosis, salt and water retention, and a catabolic state contributing to protein breakdown and lipolysis, are commonly seen following major stress in sick neonates and infants [74]. This complex of maladaptive processes may be associated with prolonged mechanical ventilation courses and intensive care unit (ICU) stay, as well as increased morbidity and mortality.

Box 15.2: Systemic response to injury

**Autonomic nervous system activation**
- Catecholamine release
- Hypertension, tachycardia, vasoconstriction

**Endocrine response**
- Anterior pituitary: ↑ ACTH, GH
- Posterior pituitary: ↓ vasopressin
- Adrenal cortex: ↑ cortisol, aldosterone
- Pancreas: ↑ glucagon, insulin resistance
- Thyroid: $J \rightarrow T_4$

**Metabolic response**
- Protein catabolism
- Lipolysis
- Glycogenolysis/gluconeogenesis
- Hyperglycemia
- Salt and water retention

**Immunologic responses**
- Cytokine production
- Acute-phase reaction
- Granulocytosis

ACTH, adrenocorticotropic hormone; GH, growth hormone; $T_4$, thyroxine; $T_3$, triiodothyronine.

The neuroendocrine stress response is activated by afferent neural impulses from the site of injury, traveling via sensory nerves through the dorsal root of the spinal cord to the medulla and hypothalamus. Anesthesia can therefore have a substantial modulating effect on this neuroendocrine pathway by virtue of providing analgesia and loss of consciousness. Outcomes after major surgery in neonates and infants may be improved when the stress response is attenuated. This was initially reported in two controlled, randomized trials comparing $N_2O/O_2$/curare anesthesia with or without fentanyl in neonates undergoing PDA ligation [75], and with or without halothane in neonates undergoing general surgery [76]. Fentanyl doses as low as 10 $\mu$g/kg may be sufficient for effective baseline anesthesia in neonates, although larger doses are necessary for prolonged anesthesia. A bolus dose of fentanyl 10–15 $\mu$g/kg has been demonstrated to effectively ameliorate the hemodynamic response to tracheal intubation in neonates [77].

It is important to distinguish between suppression of the endocrine response and attenuation of hemodynamic responses to stress. Because of their direct effects on the myocardium and vascular tone, anesthetic agents can readily suppress the hemodynamic side-effects of the endocrine stress response. The same is true when inotropic and vasoactive agents are administered during anesthesia. However, the postoperative consequences of the endocrine stress response, in particular fluid retention and increased catabolism, remain unabated. Relying on hemodynamic variables to assess the level of “stress” is therefore often inaccurate. Metabolic indices such as hyperglycemia and lactic acidosis are also indirect markers of “stress”, particularly as they are influenced by other factors such as fluid administration and cardiac output.

The effect of surgical stress has been specifically evaluated in neonates and infants undergoing cardiac surgery. Wood et al. first demonstrated a substantial increase in epinephrine and norepinephrine levels in response to profound hypothermia and circulatory arrest in these infants [78]. The hormonal and metabolic response was further characterized by Anand et al., and noted to be more extreme and distinct from that seen in adults [79]. In addition to an increase in catecholamine, glucagon, endorphin, and insulin levels, hyperglycemia and lactic acidemia persisted into the postoperative period. In an important subsequent study, Anand and Hickey compared a high-dose sufentanil technique with a combined halothane/morphine anesthetic technique in 45 neonates undergoing cardiac surgery and deep hypothermic CPB [80]. They reported a significant attenuation of hormonal and metabolic responses to surgery and bypass in the sufentanil group, with less postoperative morbidity and mortality. A conclusion from these studies supported the notion that reducing the stress response with high-dose opioid anesthesia, and extending this into the immediate postoperative period, was important to reduce the morbidity and mortality associated with congenital heart surgery in neonates.

These studies were performed over two decades ago. During the intervening period, there have been substantial changes in the perioperative care of children with heart disease as well as the management of CPB in general; along with these changes, outcomes have considerably improved. Further, it has been well demonstrated that high-dose opioid anesthetic techniques do not consistently block the endocrine stress response to cardiac surgery. To evaluate this further, however, it is necessary to separate pre-bypass and bypass responses.

**Pre-CPB**

The dose of sufentanil used by Anand and Hickey was extremely high and difficult to translate to the more common practice of fentanyl-based anesthesia. More recent studies in neonates, infants, and older
children undergoing cardiac surgery have demonstrated attenuation of the pre-bypass endocrine and hemodynamic response to surgical stimulation with a variety of anesthetic techniques. These have included: high-dose fentanyl (50 μg/kg) either by bolus or infusion [81,82], high-dose bolus fentanyl (25–150 μg/kg) with or without low-dose isoflurane [83], remifentanil infusions at various rates (0.25–5 μg/kg/min) [84], and recently even high-dose (25 μg/kg) and low-dose fentanyl (10 μg/kg) with or without dexmedetomidine (loading dose 1 μg/kg, followed by 0.5 μg/kg/h) [85,86]. Based upon the lack of significant stress responses reported in these studies, it is reasonable to conclude that there was appropriate neuraxial inhibition in these patients and that they were adequately anesthetized during this pre-bypass phase of surgery. There were no significant postoperative complications reported in the studies. It is not possible to conclude, however, that one technique is superior to another. No specific dose response between opioid plasma level and level of hormone or metabolic stress response has been established, nor has a specific benefit been demonstrated for the method or route of opioid administration, i.e., bolus or continuous infusion.

Cardiopulmonary bypass

The initiation of the endocrine stress response may be from a myriad causes and the relative contributions are speculative. Besides the surgical stimulus, additional factors include the effects of CPB, i.e. hypothermia, contact activation, hemodilution and non-pulsatile flow [87–89]. In contrast to the effect of anesthesia in the pre-bypass phase, anesthesia techniques have not been demonstrated to consistently obtund the responses to bypass [80,82,90]. This is primarily because CPB introduces a second mechanism for triggering the stress response independent of surgical stimulation, namely the acute-phase response and inflammatory cytokine release.

Cytokines are produced from activated leukocytes, fibroblasts, and endothelial cells as an early response to tissue injury and have a major role in mediating immunity and inflammation. Cytokine production reflects the degree of tissue trauma or injury. They stimulate the production of acute-phase proteins in the liver (i.e. C-reactive protein, fibrinogen, α1-macroglobulin and other anti-proteinases), stimulate the adhesion molecule cascade, increase protein catabolism and augment release of adrenocorticotropic hormone from the anterior pituitary [91,92]. In addition to direct tissue injury, exposure of blood to foreign surfaces and the systemic inflammatory response, as previously mentioned, are also potent stimuli for cytokine production and, with this, the stress response.

Effects of high-dose opioid anesthesia on stress response

Early bypass experience in neonates and infants suggested that in order to attenuate the stress response, the use of high-dose opioid anesthesia was one of the few available clinical strategies associated with an improvement in morbidity and mortality [80]. More recently, it has been shown that opioids do not in fact modify the endocrine or metabolic stress response initiated by CPB. Gruber et al. demonstrated a significant increase in stress hormone levels in infants during CPB compared with pre-bypass levels, although there was no change in plasma fentanyl concentrations [81].

Despite these findings, mortality and morbidity continue to remain low. The neonate may be more susceptible to changes in intravascular pressures, PVR and cardiac output than older children, but is nevertheless quite capable of coping with the acute phase of surgical stress. Changes in surgical practice and, in particular, the timing of surgery have altered the perioperative course of numerous defects and reduced the incidence of certain longer-term pathophysiologic consequences. Currently, it is less likely to see neonates in the immediate post-bypass period with extensive peripheral edema, anasarca or other associated complications such as impaired ventricular function, reactive pulmonary hypertension, and substantial alterations in lung compliance and airway resistance. For example, just one or two decades ago, postoperative pulmonary hypertensive crises were relatively common events in infants who had been exposed to weeks or months of high pulmonary pressure and flow, such as truncus arteriosus, complete atrioventricular canal defects, and transposition of the great arteries with VSDs. High-dose opioids were an important management component for patients at risk for pulmonary hypertensive crises. In current practice, however, these patients are operated upon at an earlier age and are therefore less likely to have significant or irreversible changes in the pulmonary vascular bed. Consequently, a strategy of high-dose opioid anesthesia to blunt the stress response may be a less critical determinant of outcome.

This is not to say, of course, that high-dose synthetic opioids are not necessary for neonatal cardiac surgery. Synthetic opioids are potent analgesics and provide hemodynamic stability due to their lack of negative inotropic or vasoactive effects. Given the limited physiologic reserve, the pathophysiologic of underlying cardiac defects and the clinical consequences of the systemic inflammatory response to bypass, an anesthetic technique that has minimal hemodynamic side-effects is clearly desirable.

The optimal opioid dose to ensure an adequate depth of anesthesia remains to be determined. In a retrospective, pharmacodynamic study of fentanyl, Hansen and Hickey demonstrated that 50 μg/kg of fentanyl was necessary to reduce the potential for sudden ventricular fibrillation in neonates with HLHS prior to CPB [93].

There are many preferences and techniques for opioid-based anesthesia in cardiac surgery. Our common practice for neonates undergoing cardiac surgery and deep hypothermic CPB is to administer up to 50 μg/kg of fentanyl prior to sternotomy, and to supplement with low-dose isoflurane titrated to hemodynamic response. During rewarming on CPB, a further 25 μg/kg of fentanyl is administered, and up to an additional 25 μg/kg fentanyl post-CPB, according to hemodynamic stability, and prior to transport to the ICU. The main aim is to provide an anesthetic that maintains hemodynamic stability and
allows the anesthesia team to concentrate on all other aspects of the surgery, bypass, and post-CPB care. Sudden changes in hemodynamics before and after bypass may develop secondary to myocardial dysfunction, residual anatomic lesions, loss of sinus rhythm, changes in preload state, variable PVR and alterations in mechanical ventilation to mention a few; using a high-dose opioid anesthesia technique allows the anesthesiologist to focus on an evolving hemodynamic picture without the distraction of side-effects from anesthetic drugs.

The risk of cardiac arrest related to pediatric anesthesia in general is increased in newborns and those with an American Society of Anesthesiologists (ASA) physical status > 3 [94–96]. The presence of underlying cardiac disease is an additional risk for cardiac arrest [96], and in the cardiac operating room the risk of anesthesia-related cardiac arrest was increased 17-fold to 21/10,000 anesthetics in a recent large series review [94]. Despite this risk, there was a low mortality associated with cardiac arrest, and this low “failure to rescue” rate is indicative of the preparation and system required to recover patients after an adverse event. It further supports the development of a dedicated cardiac anesthesia team to manage high-risk newborns during cardiac surgery. While it can be difficult to distinguish between factors contributing to cardiac arrest in newborns with underlying cardiac disease, there is an association between altered coronary perfusion and myocardial ischemia and cardiac arrest. Coronary perfusion may be reduced in patients who have uncontrolled or continuous run-off of blood flow from the systemic to the pulmonary circulation, and therefore low aortic root diastolic pressure (patients with a diagnosis of truncus arteriosus, patients with a ductus-dependent systemic circulation such as HLHS and interruption of the aortic arch or coarctation with VSD). Patients with altered coronary blood flow, such as those with pulmonary atresia, intact ventricular septum and a right ventricle-dependent coronary circulation from fistulae, are also at increased risk for ischemia. These patients have a limited ability to increase coronary blood flow when myocardial oxygen demand is increased, as is the case during periods of tachycardia, increased contractility, or wall stress in response to a surgical stimulus not blunted by an adequate depth of anesthesia.

**KEY POINTS: STRESS RESPONSE**

- Systemic response to injury from surgical trauma and interaction with CPB circuit: autonomic nervous system activation, endocrine, metabolic and immunologic effects
- Can be associated with prolonged mechanical ventilation, ICU stay and increased morbidity and mortality
- High dose opioid strategies do not consistently block neuroendocrine stress response during bypass but remain main component of anesthetic management of infants undergoing cardiac surgery

**Premature infants and very LBW neonates**

For term newborns with a weight > 2.5 kg, positive outcomes after cardiac surgery and CPB are well established, and early complete repair is currently considered the standard of care. More recently, the improving survival of premature and LBW neonates has added a new dimension to the management of CHD.

Although the technical aspects of CPB in small neonates are challenging, recent surgical advances allow routine corrective repair of complex heart disease in neonates weighing less than 2,000 g (LBWNNs). In our experience, neither gestational age nor patient size precludes successful complete repair of lesions such as tetralogy of Fallot, truncus arteriosus, and transposition of the great arteries. Survival for these LBWNNs may now approach 90% [8,9,12–15,97–99].

In addition to the physiologic limitations previously described for any newborn, the effects of the underlying cardiac disease and the implications of the surgical interventions, typical complications of prematurity have to be considered: the management of respiratory distress syndrome, fluid overload, NEC, and intraventricular hemorrhage can be extremely difficult in premature babies with CHD. Many of these complications can influence the timing and achievability of complete surgical repairs. Even with technically successful repairs in premature and LBW neonates, the effects on future development and potential need for re-interventions have not been established and will require further investigations and long-term follow-up [100,101].

**Pulmonary function**

The immature airway and lungs of premature and very LBW neonates predispose to obstruction, hypoxia, and ventilation difficulties. Lung compliance is reduced because the alveoli are primarily composed of thick-walled saccular spaces. The very compliant chest wall results in a significant mechanical disadvantage with lower FRC and O₂ reserve, lower minute ventilation, and early respiratory muscle fatigue. Dead space ventilation as a proportion of tidal volume is increased, which increases further the risk of respiratory failure. Production of surfactant begins between 23 and 24 weeks’ gestation, and may be inadequate until 36 weeks’ gestation [102]. Respiratory distress syndrome (RDS) from surfactant deficiency results in low lung volumes and poor compliance, increased intrapulmonary shunt and ventilation/perfusion (V/Q) mismatch, leading to severe hypoxia. Lung injury associated with inflammatory mediator release related to mechanical ventilation or high concentration of inspired oxygen may contribute to prolonged weaning and chronic lung disease or bronchopulmonary dysplasia (BPD). Ten years ago, a small retrospective multicenter study of premature infants with BPD and CHD evaluated the postoperative course and outcome in these LBWNNs after cardiac surgery. The overall 30-day survival post-surgery was 84%, survival to hospital discharge was 68% and there was a 50% mortality
for patients with univentricular hearts and severe BPD. Overall these patients had increased morbidity and mortality and a prolonged ICU and hospital stay compared with full-term neonates [103]. Further studies are necessary to assess the impact of newer BPD treatment strategies.

Persistent cardiac failure or excessive pulmonary flow from certain cardiac defects will increase total lung water and prevent or delay weaning from mechanical ventilation in the LBWN or premature newborn. Although RDS with increased PVR will limit pulmonary blood flow initially, as the lung injury resolves and the PVR decreases, pulmonary blood flow will substantially increase. For premature infants without RDS, pulmonary vascular tone is usually very low and pulmonary blood flow may be extremely high in cardiac defects with a large left-to-right shunt, such as truncus arteriosus. Medical management with mechanical ventilation, diuretics, inotropic support, and vasodilation is often ineffective in treating the persistent low cardiac output state with significant run-off to the pulmonary circulation. As a result, continuing conservative treatment while waiting for an appropriate weight gain is frequently not a reasonable option, and a surgical intervention is the only alternative. Palliation with a pulmonary artery band to limit pulmonary blood flow is technically challenging in LBWNs or premature infants, and subsequent distortion of the pulmonary arteries may severely complicate future surgical procedures. Therefore, complete surgical repair early in the course of management may be indicated to provide optimal conditions for growth and development.

A similar problem arises in cyanotic LBWNs or premature infants with pulmonary outflow obstruction and ductus-dependent pulmonary blood flow. A longer-term infusion of prostaglandin E₁ may be considered, but is often impractical due to the common side-effects of apnea and gastric mucosal hyperplasia. In addition, the run-off across a large ductus is difficult to control and systemic hypoperfusion may develop. Palliation with a modified BT shunt is possible, but may be limited by the size of the pulmonary arteries and geometry of the shunt. Potential problems are distortion of the pulmonary arteries or the shunt, with subsequent stenosis and poor pulmonary perfusion, or, on the other hand, excessive flow across the shunt, resulting in systemic hypoperfusion and cardiac failure from volume overload. Therefore the side-effects of palliation could further impair growth and development, and the best alternative may be early surgical repair. Some patients with tetralogy of Fallot, with or without pulmonary atresia, fall into this category and successful repair in LBWNs and premature infants has been reported (8,99). The postoperative course of these patients is often prolonged and characterized by restrictive right ventricular physiology. Nevertheless, if complete repair has been accomplished without significant residual lesion, this early anatomic correction provides the best option for longer-term survival and growth.

Premature and LBW infants with single-ventricle physiology or a parallel circulation are difficult to manage, and an adequate balance between the ductus-dependent pulmonary or systemic flow may not be achieved. Excessive pulmonary blood flow and cardiac failure often require prolonged mechanical ventilation using low inspired O₂ concentrations or adding CO₂ to the fresh gas flow in order to raise PVR. Systemic hypoperfusion (NEC, renal hypoperfusion) and feeding intolerance are common problems. As previously mentioned, a prolonged PGE₁ infusion is not desirable because of the inherent side-effects (apnea, edema, gastric outlet obstruction). Low concentrations may be used (0.01 μg/kg/min), but a clear dose–response relationship between ductal size and PGE₁ concentration has not been demonstrated. In general, size limitations are a considerable problem in newborns who require stage I palliation for conditions such as HLHS. Balancing systemic and pulmonary blood flow in a LBWN after a traditional Norwood operation where the pulmonary blood flow is supplied by a modified BT shunt can be quite challenging; the low diastolic pressure from pulmonary run-off may lead to myocardial ischemia, CHF from volume overload to the ventricle, and systemic hypoperfusion. There are alternatives to the Norwood palliation that may be preferable in the LBWN. A modified stage I operation using a right ventricle to pulmonary artery (RV–PA) conduit to supply pulmonary blood flow (Sano shunt) may allow better postoperative recovery, because pulmonary blood flow occurs predominantly during ventricular systole and therefore systemic diastolic pressures are higher. The hybrid stage I strategy is another possibility for stage I palliation in high-risk neonates (premature and LBW neonates). It does not require CPB, thereby avoiding the potential cannulation problems and risk for additional neurologic injury [104,105]. The hybrid technique is performed in the catheterization laboratory or a special angiography operating room suite: After exposure through a median sternotomy both pulmonary arteries are banded, and the patent ductus arteriosus is stented via the main pulmonary artery under fluoroscopic guidance. A large national multicenter randomized study (Single Ventricle Reconstruction Trial) compared the classical BT shunt and the RV–PA conduit regarding early death and transplantation at 1 year of age as well as several secondary outcomes (hospital course, RV function, PA size, unintended cardiovascular interventions and serious adverse events). There was a higher risk for mortality in the BT shunt group at 12 months, but no significant difference at later follow-up. Cardiopulmonary resuscitations were also more common in the BT shunt group, whereas unintended interventions and complications were more frequent in the RV–PA conduit group [106]. Although the hybrid approach reduces the initial surgical insult, there is no information on follow-up to date that any of the alternative surgical approaches described earlier lead to an improvement in longer-term survival and outcomes [16,105,107].

The potential for RDS is another important consideration for premature infants undergoing CPB. Lung injury post-cardiac surgery is triggered by shear forces and contact of blood with the non-endothelial surfaces of the extracorporeal circuit, resulting in activation of
a systemic inflammatory response [108]. In addition, significant depletion of surfactant may occur [109], and, when combined with endothelial injury, can contribute to pulmonary hypertension and altered lung compliance in the immediate postoperative period. Except for individual case reports and very small single-center studies [110,111], there are no data to support prophylactic use of surfactant, pre- or post-CPB. Nonetheless, we have occasionally used surfactant both intraoperatively and during the early postoperative period in premature infants (<36 weeks’ gestation) if there is evidence of RDS or altered lung compliance.

**KEY POINTS: PULMONARY FUNCTION IN PREMATURE AND VERY LBW NEONATES**

- There is mechanical disadvantage (reduced lung compliance, increased chest wall compliance, low FRC), surfactant deficiency, increased V/Q mismatch, and early fatigue of respiratory muscles.
- BPD and RDS may complicate management and preclude early extubation.
- There is pulmonary edema and increased work of breathing due to increased pulmonary blood flow with certain types of CHD.

**Necrotizing enterocolitis**

Congenital heart disease may be an important predisposing factor to developing NEC [112,113]. Using a case–control study of neonates admitted to a cardiac ICU over a 4-year period, McElhinney et al. reported that cardiac defects with the potential for significant run-off from the systemic to pulmonary circulation, specifically HLHS, aortopulmonary window, truncus arteriosus, and patients who had episodes of poor systemic perfusion were more likely to develop NEC [114]. This supports the notion that one of the principle underlying mechanisms of NEC in patients with CHD may be mesenteric ischemia. However, other factors, including the stress response induced by cardiac surgery and CPB-related activation of inflammatory pathways and reperfusion injury, may also play a role [112]. Of note, the feeding history or the type of feed, the use of indwelling umbilical catheters, and cardiac catheterization did not correlate with the incidence of NEC. Also, in a retrospective review of the hybrid approach for stage I palliation, Luce et al. noted that the prevalence of NEC was comparable to the data for neonates undergoing the Norwood procedure [115]. Interestingly, in another study, Miller et al. found that patients with HLHS, whose perioperative course was complicated by NEC, demonstrated lower abdominal aorta pulsatility on preoperative and postoperative echocardiograms, suggesting an inherent abnormal vasculature in a subset of these patients [116].

Although most of these cases were successfully managed medically without surgical intervention, the duration of hospitalization was significantly prolonged. The incidence of NEC reported by McElhinney et al. [114] was 3.3%, which was similar to an incidence of 3.5% reported by Cheng et al. [117], who retrospectively evaluated surgical interventions in neonates with symptomatic CHD and NEC. Patients with CHD and a diagnosis of NEC had a high mortality of 57%. However, those patients with proven NEC (without perforation) who underwent early cardiac surgery had a higher survival rate than those managed medically and with delayed surgery (75% vs. 44%).

Clinical signs of NEC include abdominal distension, feeding intolerance, temperature and glucose instability, heme-positive or frank blood in the stool, abdominal guarding, and tenderness. Abdominal radiographic examinations may demonstrate distension or an abnormal gas pattern, pneumatisis, and portal or intraperitoneal air consistent with perforation. Thrombocytopenia and leukocytosis are usually evident on blood examination. If NEC results in perforation or severe bowel ischemia, the neonate may develop sepsis syndrome with hypotension, third space fluid loss, poor perfusion, and edema. On most occasions, patients can be treated medically with fluid restrictions, antibiotics, and vasoactive support; less frequently, laparotomy may be necessary [118,119]. The key to management, however, is to improve perfusion and O₂ delivery to the splanchnic system. Therefore, once hemodynamically stable without clinical signs of sepsis syndrome, early cardiac surgical intervention to improve splanchnic perfusion is preferable.

**KEY POINTS: NECROTIZING ENTEROCOLITIS IN PREMATURE AND VERY LBW NEONATES**

- There is increased frequency of NEC in patients with CHD, with run-off in pulmonary circulation and poor systemic perfusion leading to mesenteric ischemia.
- NEC is associated with increased mortality and prolonged hospitalization.
- Early cardiac surgery can improve mortality.

**Intraventricular hemorrhage**

The risk of intraventricular hemorrhage (IVH) decreases with increasing gestational age. Currently, the general incidence of severe IVH (grade 3 and 4) is about 38% at 22 weeks and 7% at 28 weeks [102,120]. IVH in the newborn infant is determined largely by cerebral immaturity and hemodynamic disturbances, and thus even in the term infants with complex CHD there may be an increased incidence of IVH related to fluctuation in perfusion pressure, cerebral “steal” phenomena from excessive diastolic run-off, acidosis, and hypoxia. The diagnosis of IVH before surgery is important, because of the potential for extension of the hemorrhage during CPB related to anticoagulation,
increased fibrinolytic activity, and changes in perfusion pressure.

There are no prospective data suggesting an increased risk for IVH in LBW infants if they undergo early repair and CPB [12,121]. As noted previously, there is increasing data from MRI examinations of the newborn brain in the perioperative period that support the notion that the immature brain is vulnerable to injury related to cardiac surgery and CPB, particularly in watershed vascular distributions [122,123]. It is unknown whether the premature or LBW neonate has an even higher risk, and further investigations are necessary, focusing specifically on this group of patients.

As a baseline, we routinely perform a cranial ultrasound in all premature (<35 weeks’ gestation) neonates prior to cardiac surgery. There are no clear guidelines regarding the management of neonates with IVH detected by ultrasound prior to surgery. Delaying surgery as long as possible is prudent to lower the risk of extension of the bleed and additional neurologic injury. This may not be possible for all defects; however, in general, our practice is to wait approximately 7–10 days before undergoing surgery with CPB.

**KEY POINTS: INTRAVENTRICULAR HEMORRHAGE IN PREMATURE AND VERY LBW NEONATES**

- Risk of IVH decreases with increasing gestational age: the incidence of severe IVH is currently 38% at 22 weeks and 7% at 28 weeks.
- IVH in the newborn infant is determined largely by cerebral immaturity and hemodynamic fluctuations.
- There are currently no data suggesting an increased risk of developing IVH during cardiac surgery.
- There is concern regarding expansion of pre-existing IVH with surgical stress, CPB, anticoagulation, increased fibrinolytic activity and sudden changes in cerebral perfusion pressure.
- Preoperative cranial ultrasound in premature neonates is recommended.

**Outcome**

Several studies have evaluated the overall outcome of preterm and very LBW infants undergoing congenital heart surgery [8,9,12,97,99,124,125]. One of the earliest studies addressing patient size and outcome was published by Pawade et al. in 1993 [126]. They reported a hospital mortality of 16.5% for patients < 2.5 kg, with risk factors including univentricular cardiac defects and duration of CPB. Chang et al. [97] reported a 70% survival rate in 100 patients with birth weight ≤ 2500 g with congenital heart lesions. Patients were divided into three groups. Group 1 (n = 62) had early surgical intervention with a survival rate for palliation of 78% and for primary repair of 82%. Group 2 (n = 26) had late surgical intervention (at a mean age 4.3 months) after being managed medically prior to corrective surgery; 23% (6/26) died during medical management, and of the remaining 20 undergoing surgery, 90% survived. In group 3 (n = 12), no intervention was undertaken (lethal prognosis) and all patients died. The conclusion from this paper was that prolonged efforts to achieve medical stability and promote weight gain may not yield a superior result compared with early surgical intervention. Rossi et al. [6] reported their experience with 30 patients < 2 kg with CHD, citing a hospital survival of 83% and no difference in mortality rates based on age, weight, or type of surgical procedure, although premature infants tended to have an increased risk of hospital mortality. Reddy et al. [12] described a series of 102 patients who underwent complete surgical repair for CHD, with a mean weight of 2100 g, and 66 premature neonates < 36 weeks. Preoperative morbidity was more common among patients referred late for surgical correction. There were 10 early deaths, and the survival at 1 year was 82%. Regression analysis revealed no correlation between weight or gestational age with survival, but the factors that did correlate included longer bypass time, complex anomalies and diagnosis of truncus arteriosus. No patients suffered post bypass intracerebral hemorrhage.

These initial reports concentrated particularly on neonates < 2.5–3 kg. However, the size limits have been decreased even further with recent reports of successful surgery in the very LBWN. In a retrospective study, Dees et al. [127] reviewed their experience with premature LBW infants undergoing cardiac surgery. The median gestational age of their patients was 33 weeks and the mean birth weight was 1.85 kg. They noted an increased risk for NEC by a factor of 1.7, and an overall mortality twice that of patients in the neonatal ICU of similar age and size who did not have CHD. Reddy and Hanley [99] reported the outcomes of 20 infants < 1.5 kg who underwent complete repair of congenital heart defects. Modification of neonatal CPB techniques were necessary; however, there were only two early deaths unrelated to the surgical procedure. None of the patients had evidence of intracranial hemorrhage post-bypass, and at 14 months follow-up, only one late death had occurred. There were no neurological complications attributable to surgery. Repeat surgical and catheter re-interventions were necessary in four patients. Several more recent studies in LBWNs confirmed that cardiac surgery can be performed in critically ill and LBWNs with acceptable mortality, although at the cost of increased morbidity and prolonged hospital stay. Early outcome was independent of age, weight, prematurity, and type of first intervention; instead, associated chromosomal anomalies and the category of the cardiac lesion clearly influenced the risk. Primary correction appeared to result in an early survival benefit which remained constant over time [8,14,15,98,101].

A conclusion from these studies would seem to support the notion that LBW and prematurity do not appear to be
limitations to successful repair of complex two-ventricle defects, although long-term follow-up is necessary to determine growth and development patterns. However, these studies are primarily single-center studies involving relatively small numbers, which makes it difficult to draw definite conclusions. Perhaps providing a broader perspective is the relatively recent analysis from the Society of Thoracic Surgeons Congenital Heart Surgery Database (STS-CHSD), looking at the mortality in infants with LBW undergoing cardiac surgery from 2002 to 2004 [9]. The data collected from 32 centers were evaluated, and included 3,022 infants from 0 to 90 days weighing 1 to 2.5 kg (n = 517) and 2,505 infants weighing > 2.5–4 kg. Infants weighing < 2.5 kg had a significantly higher mortality following both two-ventricle repairs and single-ventricle palliation, including procedures such as coarctation of the aorta, total anomalous pulmonary venous connection repair, arterial switch operation, systemic-to-artery shunt, and the stage I palliation. Lower infant weight remained strongly associated with mortality risk after stratifying the population by Risk Adjustment for Congenital Heart Surgery (RACHS) score and Aristotle Basic Complexity levels.

As also demonstrated in this last analysis from the STS-CHSD, LBW and prematurity continue to be reported as significant risk factors for early mortality in patients with complex single-ventricle disease, in particular HLHS. Forbes et al. evaluated anatomic subtypes and preoperative physiologic variables associated with early mortality after Stage I/Norwood procedure and noted that aortic atresia, mitral atresia, a small ascending aorta, metabolic acidosis, and weight < 3 kg all increased the risk of early mortality [128]. Mahle et al. [129], in a retrospective review of 840 patients who underwent stage I surgery for HLHS, reported that surgical experience had a significant impact on outcome, with patients operated on in the later surgical era having improved survival. In addition, weight < 2.5 kg was associated with higher mortality in this study. In a retrospective review by Weinstein et al. of 67 LBWN patients with HLHS undergoing stage I/Norwood palliation (14 patients < 2 kg and two patients < 1.5 kg), early mortality, defined as death within 30 days or before hospital discharge, was 51% (34/67) [130]. Although they were unable to identify patient, procedural, or time-related variables that correlated with increased mortality, the mortality rate in this LBW group remains higher than that reported for patients of larger size who undergo stage I palliation. Another single-center outcome and risk analysis for the Norwood procedure by Stasik et al. demonstrated a 21% hospital mortality: weight < 2.5 kg and extracardiac abnormalities were independent risk factors [131].

Despite advances in surgical and CPB techniques and improved outcomes, LBWNs remain a challenging population for both surgeons and anesthesiologists. A reasonable conclusion from the studies described here would be that 2.5 kg is an important cut point, with LBWNs and premature newborns < 2.5 kg having a higher risk for mortality and morbidity regardless of the surgical procedure. In addition to size limitations, end-organ immaturity, co-morbidities, and chromosomal anomalies are important contributing factors to adverse outcomes. Careful attention to detail is essential; and the optimal management requires the close collaboration of a multidisciplinary perioperative team.

A corollary of the studies demonstrating worse surgical outcomes in neonates with lower weight undergoing cardiac surgery is that premature delivery itself is associated with significantly higher neonatal mortality. Optimal timing of delivery of neonates with CHD is now felt to be at 39–40 weeks’ gestational age; the former practice of elective delivery at earlier gestational ages (e.g., 36–37 weeks) is associated with higher mortality and should be avoided; delivery should be delayed unless there are clear maternal or fetal indications [132,133].

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**KEY POINTS: OUTCOME OF CARDIAC SURGERY IN PREMATURE AND VERY LBW NEONATES**

- Successful cardiac surgery can be performed in premature and very LBW neonates. There is potential survival benefit compared with medical management and delayed surgery.
- There is increased mortality for neonates weighing < 2.5 kg for two-ventricle and single-ventricle repair.
- End-organ immaturity, type of cardiac lesion, co-morbidities, and chromosomal anomalies are all contributing factors to adverse outcomes.

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**Fetal cardiac intervention and surgery**

Advances in fetal echocardiography have improved accuracy in the diagnosis and evaluation of congenital heart lesions and functional pathology, which has in turn led to improved perinatal management and counseling. Studies have shown, specifically for HLHS and transposition of the great arteries among other lesions [134,135], that prenatal diagnosis does result in an improved preoperative condition and possibly decreased mortality. However, there are few studies that document the natural history of cardiac growth and physiological changes in individual fetal cardiac malformations or the timing of their impact during fetal growth, and we know little about potential causes (genetic, infectious, or environmental factors). Unfortunately there is no specific animal model of cardiac malformations that is similar to the human fetus to provide insights into pathophysiology and effects on development, or to aid in developing management strategies. Nonetheless, we know that the normal development of the heart and great vessels in the fetus requires normal blood flow patterns. For example, changes in
ventricular growth and function can be seen on serial fetal echocardiograms in a fetus with aortic or pulmonary valve stenosis [136], leading to ventricular hypoplasia, fibrosis, and often abnormalities of coronary, systemic arterial, and pulmonary venous morphology [137]. In a worst-case scenario, fetal critical aortic stenosis may progress to HLHS in a proportion of cases, resulting in univentricular circulation. One of the major reasons for interventions in the fetus, therefore, is to enhance blood flow patterns to allow for better in utero development of the heart and improve postnatal outcomes. This “flow theory” is based on the concept that normal flow across the foramen ovale, atriocentricular and semilunar valves contributes to normal growth of the ventricles. Obviously, other motives for FCI include improving survival in fetuses at high risk of prenatal or neonatal death (fetal tachycardia with hydrops) and to allow recovery under the most supportive in utero conditions with periods of enhanced wound healing and myocyte proliferation [138,139] (Table 15.2).

The recognition that certain CHDs can evolve in utero and that early intervention may improve outcome has led to the evolution of FCIs [140,141]. Historically, the first FCIs were pharmacological interventions to treat fetal tachyarrhythmia or heart block. In 1975, Eibschitz et al. [142] described the use of propranolol, given to the mother, to treat fetal ventricular tachycardia. Digoxin and many other antiarrhythmic medications (sotalol, amiodarone, flecainide) followed over the years [142–147]. This transplacental pharmacotherapy is usually effective in the non-hydropic fetus. Still, fetal deaths occur in approximately 10% of all fetal arrhythmia patients, and at a higher rate in fetuses with hydrops, where occasionally direct percutaneous injection in the umbilical vein is used for refractory high-risk cases. Fetal AV block has been treated with transplacental sympathomimetic agents and/or dexamethasone (for autoimmune-related cases) [148–151]; however, the impact on outcome is not well defined. Fetal pacing has been attempted where the fetus is too premature to be delivered and other medical therapies have failed to control heart failure and hydrops [152–154], but as yet there has been no successful medium- or long-term outcome in humans.

Open FCIs involve surgical incisions into the uterus or access via a surgical trochar ≥ 3 mm in diameter as in most fetoscopic approaches. Unfortunately, incisions of this size or larger seem to be associated with an extremely high incidence of preterm labor (80%) [155]. Over the past 25 years, experimental cardiac surgery in fetal lamb and other animal models has resulted in increased knowledge of the cardiovascular and placental response to extracorporeal circulatory bypass. Fetal bypass, using the placenta as oxygenator, leads to significant post-bypass placental dysfunction with impaired fetal gas exchange, reduction in uterine blood flow, and significant fetal stress response [156–172]. Despite many problems, these models have shown that cardiac surgery on the lamb fetus with survival to full term is technically possible. So far, several successful cases of open human FCIs using fetoscopy and cardioscopy have been published [171–173], but open fetal heart surgery has only been attempted a few times [140].

Closed FCIs can be defined as percutaneous procedures in which uterus and fetus are accessed with an 18-to 19-gauge needle. To date, the main target lesions for closed FCIs are the obstruction of right-sided semilunar valve, which, if not relieved, may lead to pulmonary atresia or total anomalous pulmonary venous return, HTN, hypertension.

<table>
<thead>
<tr>
<th>Condition</th>
<th>FCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk for in utero progression</td>
<td>Balloon aortic valvuloplasty, Pulmonary valvuloplasty, Ductal stenting, Pulmonary arterioplasty and/or valvuloplasty</td>
</tr>
<tr>
<td>Fetal AS and evolving HLHS</td>
<td></td>
</tr>
<tr>
<td>PA/IVS and evolving HRHS</td>
<td></td>
</tr>
<tr>
<td>Premature closure of PDA and pulmonary HTN</td>
<td></td>
</tr>
<tr>
<td>Absent pulmonary valve with evolving bronchomalacia</td>
<td></td>
</tr>
<tr>
<td>Risk for fetal or early neonatal death</td>
<td>Maternal antiarrhythmic therapy, Maternal digoxin, Maternal sympathomimetic therapy, pacemaker, Tricuspid valve repair/occlusion</td>
</tr>
<tr>
<td>Fetal tachycardia with hydrops</td>
<td></td>
</tr>
<tr>
<td>Anomalies causing hydrops</td>
<td></td>
</tr>
<tr>
<td>Congenital heart block</td>
<td></td>
</tr>
<tr>
<td>Severe Ebstein malformation</td>
<td></td>
</tr>
<tr>
<td>Severe congenital MS with AS and intact atrial septum</td>
<td>Balloon aortic valvuloplasty, atrial septoplasty</td>
</tr>
<tr>
<td>HLHS with intact atrial septum</td>
<td>Atrial septoplasty/stenting</td>
</tr>
<tr>
<td>TAPVR with obstruction</td>
<td>Stenting of obstructed vertical vein</td>
</tr>
</tbody>
</table>

FCI, fetal cardiac intervention; AS, aortic stenosis; HLHS, hypoplastic left heart syndrome; PA, pulmonary atresia; IVS, intact ventricular septum; HRHS, hypoplastic right heart syndrome; PDA, patent ductus arteriosus; MS, mitral stenosis; TAPVR, total anomalous pulmonary venous return, HTN, hypertension.

Source: McElhinney et al. [140]. Reproduced with permission of Lippincott, Williams & Wilkins.
aortic stenosis seems to occur in the second or early third semester [182–184], and therefore at Boston Children’s Hospital, balloon dilation of the stenotic aortic valve in a fetus is performed between the 21st and 29th week of the pregnancy. Another FCI involving balloon septostomy and possibly stenting of a nearly or completely intact atrial septum in HLHS [176,179,185–187] has been used to lower pulmonary venous pressure and possibly prevent or alter the development of pulmonary hypertension and hydrops [188–190].

Fetal cardiac intervention should be considered as an innovative therapy, and careful patient selection is crucial. Currently, there is still a significant short-term risk for the fetus, unknown long-term outcomes, and also a potential risk for the mother [140]. An FCI program must be multidisciplinary, with collaboration between neonatologists, obstetricians (specialized in prenatal diagnosis and fetal medicine), pediatric cardiologists, and anesthesiologists (pediatric and obstetric). The procedures are performed in the hospital where the mother is the patient, to offer the best care for the pregnant woman.

Initially, these percutaneous techniques were performed under IV sedation of only the mother [191,192], but with technical advances and increasing awareness of the fetal stress response and pain perception [193–196], anesthesia and analgesia for both mother and fetus are now commonly provided. Various anesthesia techniques have been described for the management of the mother during fetal surgery, including IV sedation with local anesthesia, spinal and epidural anesthesia, combined techniques, and general anesthesia with single-shot intrathecal morphine for postoperative pain control [197–199]. Depending on body habitus, placental and fetal position, the surgical approach for FCIs may differ, and occasionally a regional technique with additional IV sedation may be sufficient. Unfortunately, these techniques often require extensive fluid resuscitation which, in combination with tocolytics, increases the maternal risk for pulmonary edema [200,201]. Fetal immobility and good uterine relaxation are important factors for successful FCIs, so for most cases, general anesthesia is the preferred anesthetic technique. It includes adequate aspiration and anti-emetic prophylaxis, positioning the pregnant mother supine with left lateral displacement, and rapid-sequence intubation with propofol and succinylcholine. General anesthesia is maintained with an inhalational agent alone, now often desflurane, or in combination with IV anesthetic agents [202–204], 100% oxygen, intermittent opioids, and muscle relaxant. If necessary, ephedrine or phenylephrine is used to maintain maternal blood pressure within 20% of awake baseline levels. The mother’s abdomen is prepped and draped, and after determining the weight of the fetus and using ultrasound guidance through the uterus, the obstetrician injects intramuscular atropine (20 μg/kg), vecuronium (0.2 mg/kg) and fentanyl (50 μg/kg) into the thigh of the fetus to ensure the fetus is anesthetized and immobile. The mother is monitored according to ASA guidelines, while monitoring of the fetus is usually limited to heart rate and basic contractility via ultrasound or echocardiography. Under continuous ultrasound guidance, a special 18- or 19-gauge cannula is passed through the maternal abdomen, uterine wall, and fetal chest wall into the fetal heart (either LV, RV or RA, depending on the procedure to be performed) (see Figure 15.1). Balloon positioning for inflation is based on external measurements and ultrasound imaging, and it is inflated when in the correct position [181] (Figure 15.2). Especially during procedures requiring ventricular access, fetal hemodynamic changes including bradycardia and ventricular dysfunction may occur before balloon insertion, during inflation, or even after the instruments have been removed [173]. Fetal resuscitation drugs must be immediately available. Intracardiac or intramuscular administration of epinephrine (1–2 μg/kg) and/or atropine (20 μg/kg) are used for sustained fetal bradycardia. It is important to realize that the absorption of these intramuscularly administered medications can be variable, especially in compromised fetuses. Given the high incidence of hemodynamic instability during FCIs (~45%), the latest recommendation is the prophylactic administration of epinephrine and sodium bicarbonate through the balloon catheter prior to any intervention [140]. Hemopericardium, occasionally large enough to require drainage, is another common problem during FCIs.

**Outcomes of closed FCIs**

In 1991, the first case reports of balloon dilations of fetal aortic valves were published by Maxwell et al. [191], followed by many more centers over the past 20 years. At Boston Children’s Hospital, the FCI program was started in 2000, and over 120 procedures have been performed since. There was no maternal morbidity, but about a 10% rate of fetal death or premature delivery
Similar outcomes are reported by other centers [205]. For fetuses with aortic stenosis, there are now reliable criteria to predict progression to HLHS in mid-gestation: retrograde flow in the transverse arch, severe LV dysfunction, monophasic and short mitral valve inflow, and left-to-right flow across the foramen ovale [206]. This allows for appropriate patient selection. After successful fetal aortic valvuloplasty, left heart physiology as well as aortic and mitral valve growth are improved, but not the growth velocity of the LV itself [207]. Also, moderate to severe aortic regurgitation is present in up to 40% of fetuses. On follow-up, only 30% of these patients had a biventricular circulation at birth; 8% underwent initial single-ventricle palliation and were later converted to a biventricular circulation [207]. All cases with biventricular outcome required further postnatal interventions either in the catheterization laboratory or in the operating room (atrial decompression, coarctation repair, resection of endocardial fibroelastosis or mitral valvuloplasty) Further selection criteria were developed to identify fetuses who will not be able to progress to a biventricular circulation, and who are therefore poor candidates for FCIs.

For fetuses with HLHS and intact or restrictive atrial septum, FCI has been used to improve early neonatal mortality due to restrictive outflow of the pulmonary veins and chronic venous pulmonary hypertension [190,208]. For technical reasons, fetal atrial septoplasty or stenting is more likely to be performed in the early-to-mid third trimester. In 2008, Marshall et al. reported the initial experience at Boston Children’s Hospital with fetal atrial septoplasties: 21 fetuses were treated between 24 and 34 weeks’ gestation, of whom two died, most likely from a large hemopericardium. Analysis of the 19 surviving neonates revealed that larger atrial septal defects were associated with postnatal benefits: improved oxygen saturations and less need for atrial decompression in the catheterization laboratory [186].

Fetuses with pulmonary atresia, intact ventricular septum, and evolving hypoplastic right heart can also be candidates for FCI. The z-score (number of standard deviations below normal for gestational age) of the fetal tricuspid annulus can be used to predict the potential growth of the RV and therefore chances for a biventricular circulation [209]. Several groups have reported their experiences with fetal pulmonary valvuloplasty [177,210,211]. The Boston FCI group published their preliminary results in 2009 [212]. Balloon dilation of the pulmonary valve was attempted in 10 fetuses during mid-gestation. After an initial four technically unsuccessful procedures, the following six were successful and the fetuses demonstrated ongoing growth of the tricuspid and pulmonary valve annulus as well as the RV. The authors concluded that fetal valvuloplasty is technically possible but is associated with a significant learning curve and requires careful patient selection, especially given the generally encouraging outcomes for patient with PA/IVC [213].

In summary, FCIs are technically feasible and can improve short-term outcome in selected patient groups, but are associated with significant risk of fetal death or premature birth (≈10%) and the potential for maternal harm. Long-term benefits are still to be determined, and the discussion regarding biventricular repair at all costs vs. univentricular palliation is ongoing. Further advances in imaging and equipment technology will allow better patient selection and earlier, possibly even more complex, interventions. Systematic short- and long-term outcome data will be important to assess the effectiveness and safety of FCIs.

**KEY POINTS: FETAL CARDIAC INTERVENTIONS AND SURGERY**

- Fetal cardiac interventions can be classified into pharmacological, open, and closed interventions.
- The rationale for FCI is the prevention of fetal or early neonatal death and/or ventricular hypoplasia in cases of critical aortic or pulmonary valve stenosis via restoration of normal blood flow patterns.
- Currently, percutaneous closed interventions, using 18- or 19-gauge access cannulas, guidewires, and balloon catheters, are mainly used to treat selective patient groups with documented short-term benefits:
  - Fetal aortic stenosis with evolving HLHS
  - Fetal PA/IVS with evolving hypoplastic right heart
  - Fetal HLHS with intact or highly restrictive atrial septum.
- FCI is associated with a 45% risk of significant intraoperative hemodynamic instability requiring fetal resuscitation and a 10% risk of fetal death or premature delivery.
Selected references

A full reference list for this chapter is available at:
http://www.wiley.com/go/andropoulos/congenitalheart


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CHAPTER 16
Approach to the Adult Patient

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Introduction

Pediatric cardiology and pediatric cardiac surgery went through a period of rapid growth in the 1960s. Continued growth and development of centers of excellence in the subsequent decades created a population of teenagers and young adults living with congenital heart disease (CHD) [1]. These centers vary in their delivery of care to the patient over 18 years of age and there is still a great deal of work to be done in organizing and monitoring the care and outcomes of the teenaged and adult patient. Many established pediatric centers continue to manage the cardiac lesions of adults living with CHD, with acknowledged reluctance to refer to an adult cardiologist. Reasons for failure to refer to an adult center include emotional attachment on the part of the patient, family and cardiologist, as well as a perceived lack of qualified adult congenital heart disease (ACHD) cardiologists with appropriate institutional support. Triggers to initiate a referral to an adult center include reaching the age of majority, graduation from college, marriage, pregnancy, and development of an adult co-morbidity [2]. While established ACHD centers of excellence exist with transitioning programs from the pediatric to adult centers, they are inadequate in number, and the ACHD programs must compete for resources with the coronary disease patients, valvular heart disease patients, and cardiomyopathy and heart failure patients. There is an acknowledged but unfortunate loss of follow-up in spite of these transitioning programs, which can be attributed in part to lack of resources, lack of health insurance, and distance to travel to a regional center of excellence [3,4]. A comprehensive survey of ACHD patients in North America identified that 42% of patients (mean age 19 ± 9.1 years) had gaps in care of > 3 years. This survey excluded adults cognitively incapable of responding directly to the survey and probably underestimates the gaps in care. The most common reasons cited for gaps in care were “feeling well,” “changing or losing insurance,” and “financial problems” for severe cardiac lesions. For milder lesions, “lost track of time” and “decreased parental involvement” were the most common reasons. Geography was the most significant predictor of being lost to regular cardiology care [5]. Many ACHD patients perceive themselves as normal individuals who have had a heart problem in the past that is “fixed,” and fail to appreciate the need for follow-up.

The burden of ACHD patients will increase. In a comprehensive prevalence study in the province of Quebec, the median age of all individuals with severe ACHD in 1985 was 11 years, and in 2000 it was 17 years. In 2000 the median age of all adults living with CHD was 40 years. In the era around 2000, the numbers of adults living...
with severe CHD exceeded the number of children living with severe CHD, and the ratio continues to rise in favor of adult populations [6]. One of the largest European ACHD centers has recently published their experience of a nine-fold increase in patients > 60 years from 2000 to 2012 [7].

Anesthesiologists working in these adult centers will have the core competencies to deal with ACHD patients, but they must be mindful of the issues unique to this population, and ideally should be a component of a multidisciplinary team. This expertise is not limited to the operating room but should also be available in the preoperative optimization and planning, postoperative monitoring, and pain management. Anesthesiologists vary in their knowledge of CHD. A survey of one of the largest academic anesthesia departments in North America revealed variable knowledge of CHD in its providers, with pediatric anesthesiologists showing the highest degree of knowledge, ahead of fellowship trained and certified cardiac anesthesiologists [8]. Increasingly, services provided to this population will occur in the interventional suite, electrophysiology suite, and echocardiography laboratory, in addition to the cardiac operating room and cardiovascular intensive care unit (ICU). The vast majority of these patients will require an intervention or surgery for a previously palliated lesion. Cardiac and non-cardiac sequelae of the lesion and previous interventions will frame the anesthetic considerations and, in many cases, limit the options available to the patient. The ACHD population is a challenging group of patients that features prominently in board and international specialty certification examinations.

**Non-cardiac sequelae of CHD**

**Pulmonary sequelae**

The ACHD patient population has diminished static lung function and a reduced capacity to augment cardiac output in response to stress [9]. Restriction does not occur in the absence of surgical interventions; the degree of restriction rises with surgical intervention at an early age, as well as the number of chest incisions, particularly if the patient has had both thoracotomy and sternotomy, with over 50% of these patients having restricted spirometry testing profiles [10]. They are more likely to have a decreased exercise tolerance based on oxygen consumption ($VO_2$) index, diminished forced expiratory volume in 1 second ($FEV_1$) and forced vital capacity (FVC), and significant restriction compared with normal [11] (Figure 16.1). Mechanisms responsible are thought to include diaphragmatic palsy, lung scarring, and chest wall deformities. Although restriction is less likely to affect the ability to ventilate the patient intraoperatively, diminished pulmonary function may have consequence in the recovery room or ICU, and the ability to wean from the ventilator. When considering a revision of a previously palliated lesion in a patient with significant restriction, discussion of prolonged ventilator wean and possible tracheostomy should take place in the preoperative visit. Increasingly, adults present with $FEV_1$ and FVC ratios that are incompatible with a surgical intervention utilizing neuromuscular blockade and controlled ventilation; catheter-based solutions using spontaneous ventilation techniques will have to be considered. Moderate to severe impairment of FVC is a predictor of mortality in adults with CHD [12]. The inability to augment cardiac output in response to stress is a major consideration for patients contemplating pregnancy, as well as those experiencing sepsis, with or without non-cardiac surgery. Figure 16.2 shows a representative patient with severe pulmonary sequelae.

**Pulmonary hypertension**

Pulmonary hypertension is a major perioperative risk factor, but it is not as difficult to manage as acquired primary pulmonary hypertension [13]. Pulmonary hypertension associated with CHD can be classified into four groups [14]:

1. **Systemic-to-pulmonary shunt with increased pulmonary vascular resistance (PVR)**. These shunts may be unrestricted atrial septal defects (ASD), ventricular septal defects (VSDs), patent ductus arteriosus (PDA), or surgically created shunts such as the Blalock–Taussig, Waterston, and Potts’ shunts. A long standing left-to-right shunt with a pulmonary-to-systemic flow ratio ($Q_p:Q_s$) exceeding 2:1 creates shear stresses and changes in the endothelium, and subsequent hypertrophy of the smooth muscle.

2. **Eisenmenger syndrome**. Long-standing systemic to pulmonary shunts will lead to systemic pulmonary pressures and reversal of the shunt to right-to-left, and cyanosis will ensue.

3. **Primary pulmonary hypertension attributed to CHD, and yet the CHD lesion is quite mild**. The CHD lesion is quite minor, such as a small ASD, and not the cause of pulmonary artery hypertension (PAH). There is probably another etiology of the PAH.

4. **Pulmonary hypertension due to left heart disease**. Causative lesions include a regurgitant systemic atrioventricular (AV) valve, aortic insufficiency (AI), or a failing systemic ventricle.

Anesthetic management and strategies for weaning from bypass must be tailored to the underlying cause of PAH in the ACHD patient. The low incidence of symptomatic pulmonary hypertension post-repair makes it difficult to justify routine placement of a pulmonary artery (PA) catheter. The decision to place a PA catheter can be made in the operating room when the PA pressures are ~60% of the systemic pressures. When used in centers accustomed to their placement, the morbidity is low; however, the presence of the catheter can sometimes delay the progress of the patient in the ICU who is otherwise progressing well. Strategies to manage pulmonary hypertension include avoidance of vasoconstrictive triggers,
minimizing PVR with oxygenation, alkaline pH, minimal tidal volumes or spontaneous modes of ventilation, and the use of the pulmonary vasodilators nitric oxide, inhaled prostacyclin (PGL₂), and, in the process of weaning in the ICU, oral sildenafil [15]. The underlying cause must be addressed; a patient with a long-standing left-to-right shunt and elevated PA pressures will respond to pulmonary vasodilators, whereas the patient with severe systemic AV valve regurgitation in the failing right ventricle (RV) of a congenitally corrected transposition of the great arteries (ccTGA) will also need inotropic support and systemic afterload reduction.

Eisenmenger syndrome is a challenge, as the anaesthesiologist must deal with both the pulmonary hypertension and the potential to exacerbate the right-to-left shunt, resulting in worsening cyanosis. It is more likely to present in patients with large and complex septal defects. The demographics of the syndrome are changing, with increased prevalence in the adult population [16]. The median survival after diagnosis of Eisenmenger syndrome is reported to be 35–60 years [17–19]. Patients with Eisenmenger syndrome will present for heart–lung transplantation, but outside of this context, interaction with an anaesthesiologist will be limited to diagnostic investigations and non-cardiac surgery. Although there have been advances in medical management with oral pulmonary vasodilators, the progress is limited to improvement in the measured PVR at cardiac catheterization and a mild improvement in the 6-minute walk test [14]. The overall risks for anesthesia remain unchanged. Generally, Eisenmenger patients are much easier to manage than primary pulmonary hypertension patients, as the RV is robust and accustomed to a high afterload. There is an exhaustive three-part publication, coauthored by six directors of ACHD centers in North America, Europe, and Japan with management recommendations [20–22]. Chapter 28 contains an extensive discussion of pulmonary hypertension.
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Figure 16.2  A 26-year-old with pulmonary atresia and right ventricle (RV) to pulmonary artery (PA) conduit. The patient's weight is 45 kg, and the previous history includes pneumonectomy at age 16 years, paralyzed vocal cord, asthma, bronchiectasis, kyposcoliosis. Forced expiratory volume in 1 second (FEV$_1$) is 600 mL (20% of normal). The patient has RV–PA conduit obstruction with an RV pressure of 48/25 mmHg, and elevated pulmonary vascular resistance at 8–10 Wood units.

Hematological sequelae
Patients with cyanotic heart disease have erythrocytosis, an increase in the red cell line in response to hypoxia. Relative to the red cells there is a deficiency in vitamin K-dependent clotting factors, fibrinogen, and platelets [23]. Ironically these patients have an increased risk of thrombosis yet are frequently coagulopathic intraoperatively [24,25]. Phlebotomy is inappropriate unless there are extreme symptoms of hyperviscosity, as iron deficiency with microcytosis is an independent risk factor for stroke, thrombosis and hemoptysis [26,27].

Renal sequelae
Impaired renal function, as in patients with acquired heart disease, is a significant predictor of morbidity and length of stay in pediatric and adult populations undergoing congenital cardiac surgery [28,29]. Pediatric post-surgical patients with acute kidney injury who recover from renal dysfunction requiring dialysis frequently have markers of renal insufficiency [30]. A more recent study found an incidence of acute kidney injury requiring dialysis of 2.9% (84/2994), and a correlation with postoperative mortality (35/84). Of the remaining 41 survivors, 15 died of non-renal causes, and there was evidence of long-term renal insufficiency in only one of the 26 long-term survivors followed for a period 3.5–10.5 years [31]. Some of the difficulty in assessing the degree of renal insufficiency lies in the lack of uniform definitions. The Acute Dialysis Quality Initiative Group has defined the range of renal dysfunction using the so called “RIFLE classification system” (Box 16.1) [32], which has been endorsed by the Multi-societal Database Committee for Pediatric and Congenital Heart Disease, and further subdivided into renal insufficiency and renal dysfunction [33]. A total of 1,102 adult patients attending the Royal Brompton Hospital in London over a period between 1999 and 2006 had a serum creatinine measured and a glomerular filtration rate calculated. Renal dysfunction was mild in 41% of patients, and moderate or severe in 9%. Not surprisingly, severe renal impairment correlated with increased mortality over the 4-year follow-up period [34].

Box 16.1: The RIFLE classification system
- Risk (R) – 1.5-fold increase in serum creatinine, > 25% decrease in glomerular filtration rate, or urine output < 0.5 mL/kg/hour for 6 hours
- Injury (I) – two-fold increase in serum creatinine, > 50% decrease in glomerular filtration rate, or urine output < 0.5 mL/kg/hour for 12 hours
- Failure (F) – three-fold increase in serum creatinine, serum creatinine > 4 mg/dL, > 75% decrease in glomerular filtration rate, urine output < 0.3 mL/kg/hour for 24 hours, or anuria for 12 hours
- Loss (L) – persistent acute renal failure defined as the need for renal replacement therapy for > 4 weeks
- End-stage renal disease (E) – need for renal replacement therapy for more

Source: Welke et al. [33]. Reproduced with permission of Cambridge University Press.

Neurological sequelae
Adults currently living with CHD are from an era where the developing brain was subject to the consequences of untreated cardiovascular disease, due to the nature of their defect and the lack of surgical interventions available to infants and small children at the time. Profound cardiogenic shock at presentation and living with cyanosis have significant effects on the developing brain [35]. Surgical, perfusion, and interventional strategies were developed for early intervention in the neonate, with improved survival but with a concerning incidence of neurodevelopmental complications in survivors. A recent cohort of 131 infants having had cardiac surgery requiring cardiopulmonary bypass (CPB) were assessed at surgery, at discharge after surgery, 12–18 months later, and at 5 years of age. There was significant developmental delay in children with cyanotic and non-cyanotic lesions, and persisted to the age of school entry [36]. These complications may be undetectable at the time of discharge from hospital, and yet will become apparent over time. Sequelae in earlier eras of congenital heart surgery are even more significant. They include sensorineural complications (blindness, deafness), stroke (both thrombotic and hemorrhagic), seizures, and developmental delay.
Cerebral abcess is a known complication of complex cyanotic heart disease, but may not be associated with long-term neurological sequelae when appropriately managed. These adverse outcomes are not attributable solely to operating room events, but are a consequence of living with cardiac diseases [37]. A comprehensive review from the Mayo Clinic of 162 adults over 18 years of age with cyanotic heart disease found that 13.9% (22/162) had a cerebrovascular event. Factors that were significantly associated with a cerebrovascular event were the presence of atrial fibrillation, hypertension, history of phlebotomy, and microcytosis. Although this study addressed the incidence in cyanotic heart disease, it is interesting to note that the use of antiplatelet agents and/or warfarin did not show any statistically significant decrease in the incidence of cerebrovascular events [27].

Adults with developmental delay and known syndromes with limited cognitive function are probably accustomed to inhalational inductions and the presence of a care-giver or parent. Adult centers accepting these patients in transition will have to acknowledge and accommodate some aspects of the pediatric practice. Inhalational inductions are less practical, and premedication with hypnotics, and occasionally intramuscular ketamine, may be necessary. Patients’ impressions made on the first anesthetic encounter at the adult facility will influence future attitudes towards anesthetic care, and compliance with future visits.

**Hepatic sequelae**

Hepatic congestion, dysfunction, and cirrhosis with the resultant esophageal varices are a major source of morbidity for adults living with Fontan and Glenn cavopulmonary connections, tetralogy of Fallot (TOF) with a failing RV, and Ebstein’s anomaly. This is frequently multifactorial, due to transfusion-related hepatitis C, congestion from high right atrial (RA) or cavopulmonary pressures, and low cardiac output. The hepatic dysfunction will not improve without lowering the RA or central venous pressure (CVP), and yet its presence often precludes the patient from being listed for heart transplant or being considered for a cardiac surgical intervention [38]. A retrospective examination of a cohort of 96 Fontan outpatients, the majority over 18 years of age, was performed at the Boston Children’s Hospital. Creatinine and bilirubin were measured and then matched to controls of patients with hepatitis C cirrhosis. Model for End-stage Liver Disease (MELD-XI) scores, excluding international normalized ratio (INR) scores, were examined. The advantage of the MELD-XI score is that the INR is excluded, and many patients with the Fontan circulation are taking warfarin. They found that Fontan patients exhibit a similar MELD-XI score distribution to that of a cohort of patients with established liver cirrhosis due to hepatitis C infection. The patients with MELD-XI scores > 18 had a substantially higher risk of sudden cardiac death, death from congestive heart failure, and cardiac transplantation [39].

The dilemma for the CHD team is how to risk-stratify patients with cirrhosis for cardiac surgical intervention, e.g., pulmonic valve replacement for a failing RV in a TOF patient with free pulmonary insufficiency, or conversion of an RA to PA connection Fontan to a cavopulmonary anastomosis, or transplantation. Involvement of the hepatology service, transjugular liver biopsy, and measurement of the transhepatic gradient have all been helpful in assessing the extent of hepatic dysfunction, as well as the potential for improved hepatic function with lowering of the venous pressures and improved cardiac output. Proceeding with cardiac surgery in the face of significant hepatic dysfunction will expose the patient to massive transfusion due to the lack of hepatic synthetic function of coagulation factors. The exposure to multiple blood transfusions may sensitize patients to minor red blood cell antigens and handicap them in the future for consideration of heart transplantation. This predicament leaves the ACHD team with the difficult decision of whether to optimize patients’ hemodynamics with significant operative morbidity and risk of mortality or to accept the risk of medically managing their heart failure in the hope of listing them for a heart transplant. This is currently an unresolved and difficult management issue for multidisciplinary ACHD teams.

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**KEY POINTS: NON-CARDIAC SEQUELAE OF CHD**

- Adults with CHD can experience a wide range of non-cardiac sequelae:
  - Pulmonary – restrictive lung disease, pulmonary hypertension
  - Hematological – erythrocytosis, polycythemia, coagulopathy
  - Renal dysfunction – mild in 41%, moderate or severe in 9%
  - Neurological sequelae – developmental delay, cerebral abscess, stroke, early dementia
  - Hepatic sequelae – hepatic congestion, dysfunction, and cirrhosis from right heart failure or elevated cavopulmonary pressures.

**Vascular access considerations**

There are a number of challenges with arterial and venous access due to patient factors related to stature and syndromes, previous vascular cut-downs and femoral vessel cannulation, vascular thrombosis, or absence of central veins. The preoperative visit should include examination of the extremities for cut-down scars and measurement of blood pressure in both arms and, if necessary, a leg. Planning for major cardiac surgery should include venous Doppler studies of central veins, and arterial and venous
studies of the femoral vessels. Discussion in a preoperative briefing about access and plans to emergently cannulate the femoral vessels in the event of a cardiac injury at sternotomy is mandatory. Adherence to institutional infection control guidelines while placing the lines is essential. Infective endocarditis guidelines have lessened, but are still indicated in patients with prosthetic material, palliative shunts or conduits within the first 6 months of surgery or implantation, and remain indicated if there is a residual lesion in close proximity to the repair [40]. An example is an AI jet directed at a VSD patch in a repaired TOF.

Unrestricted shunts

Patients with simple unrestricted shunts, such as ASDs, VSDs, large PDA s, and aortopulmonary collaterals will have a left-to-right shunt in the presence of normal or low PVR, and pulmonary blood flow may exceed systemic blood flow. Patients with complex congenital lesions may have had a systemic-to-pulmonary artery shunt (e.g., Blalock–Taussig, Waterston–Cooley, or Potts’ shunt) as a palliative procedure to augment pulmonary blood flow and may have unilateral PAH. A recently created Australian National registry for PAH in ACHD found that, of the first 50 registrants, 47 had systemic-to-pulmonary artery shunts [41]. At rest, breathing room air, these patients may have a 2:1 or as much as a 3:1 shunt ratio of pulmonary to systemic blood flow. A common error is that an anesthesiologist, being concerned about the patient’s heart disease, will ventilate the patient on 100% oxygen and unintentionally lower the patient’s PVR, converting a 2:1 shunt to a much more severe imbalance such as a 4–5:1 shunt, and ironically the acyanotic patient will have a metabolic acidosis from diminished systemic oxygen delivery. Unrestricted left-to-right shunts have the potential to reverse with a profound decrease in the systemic vascular resistance (SVR). A well-intentioned attempt to avoid a general anesthesia in a patient with a common atrium by using a neuraxial anesthesia technique may trigger profound hypoxemia that may be difficult to reverse. Figure 16.3 presents an Ebstein’s anomaly patient with a right-to-left shunt inferior to an Amplatzer™ device post-induction.

Cyanotic heart disease patients with single ventricles and pulmonary circulation supplied by aortopulmonary collaterals have a precarious balance between pulmonary blood flow and systemic oxygen delivery. The coronary circulation is dependent on the diastolic pressure, and will compete with the run-off into the pulmonary circulation when a patient is anesthetized and hyperventilated with 100% oxygen with a low PVR. After induction the anesthesiologist should attempt to maintain the patient on an FiO2 that recreates their room air oxygen saturations at rest. Ventilation should be at lung volumes that are close to functional residual capacity (FRC) and maintain a normal PaCO2.

Pregnancy

As part of a large comprehensive prospective observational trial of consecutive pregnant woman with cardiac disease receiving care at the University of Toronto between 1997 and 2007, 405 pregnancies in 318 women with CHD were studied prospectively and were subsequently available for retrospective study of late cardiac events [42]. In the larger 2001 study, the investigators enrolled 562 consecutive pregnant women with heart disease (CHD and acquired) and determined the outcomes of 599 pregnancies not ending in miscarriage. They found a 13% incidence of adverse events, and developed a risk score called the Cardiac Disease in Pregnancy Score (CARPREG), which is widely utilized in multiple centers for women with cardiac disease outlined in Box 16.2 [43,44]. Siu et al. compared the prospectively gathered data on the 318 women with CHD, and later retrospectively reviewed their cases for the risk factors for a late cardiac event. The risk factors found to be predictive of a cardiac event during pregnancy (CHD and acquired heart disease) are presented in Box 16.2 [45]. The risk factors for a late cardiac event in women with CHD following pregnancy are listed in Box 16.3 [44].

A larger retrospective review of pregnancy outcomes, 1802 pregnancies in 1302 women with CHD, in a combined study from Belgium and the Netherlands, found a lower incidence of cardiac complications (7.6%). The most common were arrhythmias (4.7%) and congestive heart failure (1.6%). Like the CARPREG study they found cyanotic heart disease, the use of cardiac medications before pregnancy, and left heart obstruction as predictive of a maternal cardiac event. They also found the presence of a mechanical valve (aortic or mitral) and systemic AV valve regurgitation in the context of complex CHD to be additional risk factors for a maternal cardiac event. A major limitation of this study was that the institutional review board prevented the investigators from contacting...
Box 16.2: Risk factors found to be predictive of a cardiac event during pregnancy

**CARPREG risk score: predictors of maternal cardiovascular events**
- New York Heart Association (NYHA) functional class > II
- Cyanosis (room air saturation < 90%)
- Prior cardiovascular event
- Systemic ventricular ejection fraction < 40%
- Left heart obstruction (e.g., mitral valve area <2 cm² or aortic valve area < 1.5 cm², or left ventricular outflow gradient > 30 mmHg)

**CARPREG risk score: for each CARPREG predictor that is present, a point is assigned**
- Risk estimation of cardiovascular maternal complications
  - 0 points – 5%
  - 1 point – 27%
  - >2 points – 75%

Source: Siu et al. [43]. Reproduced with permission of Lippincott, Williams & Wilkins.

Box 16.3: Risk factors for a late cardiac event (LCE) in women with congenital heart disease following pregnancy

- LCE occurred in 50/405 (12%) pregnancies in 318 women with CHD
- 5-year rate of LCE was higher in:
  - Women with adverse events during pregnancy
  - Functional limitations or cyanosis
  - Subaortic ventricular dysfunction
  - Subpulmonary ventricular dysfunction or significant pulmonary regurgitation
  - Left heart obstruction
- Patients who had more than one risk factor above had a risk of LCE of 44% (+10%)

Source: Balint et al. [42]. Reproduced with permission of the BMJ.

or reviewing the charts of the deceased patients, and patients who did not provide written consent were not included in the study [44].

There are several cases series of patients with specific congenital cardiac lesions or a cluster of similar congenital cardiac lesions, with favourable outcomes in right and left ventricular outflow tract lesions [46–52]. Risk stratification for maternal and neonatal outcomes can be accomplished with exercise testing. Lack of a chronotropic response to exercise is predictive of both maternal and neonatal events [53]. Ideally, pregnancies are planned after consultation with a congenital cardiologist and high-risk obstetrician in the context of a tertiary care program; however, for reasons outlined in the introduction this will not always be the case. Once pregnancy is confirmed, a patient should be referred to a tertiary care program with expertise in pregnancy in ACHD as soon as possible, and in the case of a high-risk mother, a cardiovascular intensivist should be consulted early in the planning stages [54]. Patients may present in second and third trimesters for cardiac interventional procedures and/or subsequent cardiac surgical intervention. Ideally cardiac catheterization procedures will occur after the fourth month when organogenesis is complete. The uterus must be double-shielded from radiation exposure during catheterization. There should be appropriate fetal monitoring, both for an intervention if the fetus is the age of viability and to optimize hemodynamics in response to fetal distress. The attending anesthesiologist must be a cardiac anesthesiologist with congenital heart expertise, with cardiac surgery and perfusion on standby, and appropriate ICU resources available for the mother and fetus. Cardiac surgery in the mother can be urgent, as in the case of left ventricular obstruction with symptoms at rest, or emergent, as in the case of an aortic dissection in a woman with Marfan syndrome or a thrombosed mechanical systemic AV valve.

As in the instance of the interventional cases, appropriate fetal monitoring should be utilized for cardiac surgery. Normothermic perfusion, mean arterial pressure (MAP) > 70 mmHg, minimal CPB times, and bypass pump flows > 2.5 L/min/m² are optimal. Hypocapnia, which ordinarily may be used for patients who are dependent on a low PVR (TOF, Ebstein’s anomaly, and Fontan circulation), has adverse effects causing uteroplacental vasoconstriction and fetal hypoxia, and should therefore be avoided. If the fetus has reached the age of viability, a cesarean section should proceed prior to the cardiac surgery, if the cardiac surgery is urgent [54,55].

Anticoagulation of a pregnant CHD patient with a mechanical heart valve is a major source of anxiety and controversy. It will present management problems not only for the cardiologist and obstetrician but also for the anesthesiologist assigned to manage elective, urgent, and emergent procedures during the pregnancy, as well as at delivery, whether it is vaginal or surgical. In the study from Belgium and the Netherlands described earlier, all the patients with mechanical heart valves had complications. Two patients experienced thrombosed mechanical valves while transitioning from therapeutic full-dose low-molecular-weight heparin (LMWH) to oral anticoagulation [44]. Investigators from the University of Toronto examined a subset of their larger study and found 23 women with left-sided mechanical valves who were treated with LMWH and low-dose aspirin: 15 mitral valves, nine aortic valves, and one with both. There was one maternal thromboembolic event (4%), which resulted in maternal and fetal death. Although there was a much lower incidence of thrombosis, there was a an elevated risk of cardiac events (22%), adverse neonatal outcome (43%), and post-partum hemorrhage (14%) [56].

A similar observational trial from 2003 to 2011 in Bristol, UK, examined all pregnancies in women with mechanical heart valves, 32 pregnancies in 15 women with a combination of acquired heart disease and CHD. Four pregnancies used only LMWH, 22 used warfarin...
alone, and six used a combination of the two. The warfarin patients were transitioned to LMWH at 36 weeks. The combination group were started on LMWH at 4–6 weeks until 13 weeks’ gestation and transitioned to warfarin until 36 weeks, and were again put on LMWH at 36 weeks. All groups had anti-factor Xa levels monitored appropriately. All 4 LMWH patients experienced a maternal event, and one also had a fetal death. Two of the four LMWH patients had thrombosed valves (one mitral, one Ebstein’s) requiring emergent delivery and cardiac surgery; the third patient presented at 7 weeks’ gestation with a fatal intracerebral hemorrhage, and the fourth patient delivered successfully at 38 weeks but had a massive hemorrhage 6 days postpartum. Successful fetal outcomes were seen in 75% of cases in the LMWH group, in stark contrast to the warfarin group, which had only 23% (5/22) successful fetal outcomes. All of these fetal losses occurred in the first and second trimesters. The fetal losses in the warfarin group were very high, but they also experienced a low maternal event rate of 13% (3/22), and all were hemorrhages in the same patient in three separate pregnancies (two miscarriages and one delivery). The combination group of LMWH and warfarin (6/32) experienced one transient ischemic attack at 9 weeks while on LMWH, and the patient was transitioned to warfarin at that time. Fetal loss occurred in 50% (3/6), all while on warfarin and prior to 20 weeks’ gestation, and 17% (1/6) had maternal haemorrhage [57].

Management of the ACHD patient for labor and delivery must take into account the physiological changes of pregnancy, and how they will impact the specific congenital heart lesion. Lowering of the SVR will favor regurgitant lesions such as an adult repaired TOF with pulmonary regurgitation. The process of labor with uterine contractions is a challenge for patients with obstruction of the systemic ventricle or valvular aortic stenosis; each uterine contraction mobilizes ~300–500 mL into the intravascular space. Generally vaginal delivery is preferable, with vacuum or instrumental assist in the second stage to avoid a Valsalva maneuver. Carefully titrated epidural anesthetics are possible with a reduced crystalloid intravascular volume loading infusion. One must keep in mind that afterwards, when the epidural anesthetic dissipates, the patient will have an increase in circulating blood volume that should be anticipated with diuretics. The sudden hemodynamic changes with a spinal anesthetic make this technique unsuitable for ACHD patients undergoing vaginal or caesarean delivery, aside from the milder lesions, and it is absolutely contraindicated in any patient with the potential to reverse a left-to-right shunt or exacerbate a bidirectional or right-to-left shunt. Cardiac anesthesiologists are very comfortable with and biased toward a general anesthetic for elective caesarean section, whereas an obstetrical anesthesiologist is more likely to be comfortable with a regional technique. The patient’s preferences should be taken into account where possible. Appropriate ICU resources for the mother and fetus must be immediately available, and caution should be exercised in discharging the patient too early to the labor recovery ward. Monitoring cardiac rhythm with telemetry in the postpartum period is advised.

### KEY POINTS: PREGNANCY IN ACHD

- Pregnancy in ACHD is associated with a 7–13% incidence of adverse cardiac events.
- Cyanotic heart disease, left heart obstruction, mechanical valve, and pre-pregnancy cardiac medications are risk factors.
- Fetal loss and complications after birth are more common in ACHD.
- Multidisciplinary planning, fetal monitoring, and backup plans for maternal or fetal instability are necessary for anesthesia during pregnancy.
- Anticoagulation during pregnancy is problematic, with low-molecular-weight heparin preferable to warfarin for maternal and fetal outcomes.
- Vaginal delivery is preferable; neuraxial techniques can be utilized with careful titration and hemodynamic monitoring.

### Adults with Down syndrome

In a sample of 10 states in the USA, the birth rate of infants with Down syndrome increased from 9.0/10,000 live births in 1979 to 11.8/10,000 live births in 2003, and the prevalence in children aged 0–19 years in the same group was 10.8/10,000 [58]. The investigators later retrospectively reviewed the same population and found the overall survival rates at 1 month, 1 year, 5 years and 20 years to be 98%, 93%, 91%, and 88%, respectively. With the exception of outcomes at 1 month, overall survival at all other ages improved over the time of the study [59]. Similar birth rates in Norway (11/10,000 live births) and Sweden (13.1/10,000 live births) were recently reported, with the median age at death now reaching 60 years [60,61]. Around 40–50% of patients with Down’s syndrome have CHD, most commonly AV canal defects (37%) [62]. The improvements in mortality are largely attributed to improvements in the management of CHD in this population, and attitudinal changes towards the care of these patients. Hospitalization rates in the USA, using the Nationwide Inpatient Sample from 1998 to 2009 for adults with and without Down syndrome aged 18–64 years, revealed that 11.5% of all hospital admissions (9,088/78,793) for CHD were patients with Down syndrome. Patients with Down syndrome had higher in-hospital mortality (odds ratio 1.8) and were less likely to have cardiac procedures or surgery.
(odds ratio 0.3) [62]. Down syndrome patients in this study were also more likely to have cyanosis, secondary polycythemia, heart failure, and pulmonary hypertension. The authors infer but cannot prove that patients in the Down syndrome group had a higher prevalence of unrepaired defects, reflecting a lower rate of early repair in childhood.

With the median survival of all patients with Down syndrome near 60 years, including patients with CHD, the adult cardiac anesthesiologist will increasingly encounter this population. It is highly likely that this population will increase. The Down syndrome patient will likely live with family members or in an assisted living environment. Co-morbidities include deficiencies in cognition and tendency towards infection. Dementia may occur as early as 40 years, and the prevalence of dementia is 50–70% at 60 years. Other issues include acquired mitral valve disease, atlanto-axial instability, obstructive sleep apnea, and epilepsy [63]. The preoperative visit must include a thorough history, assessment of atlanto-axial instability with recent flexion and extension views of the cervical spine, and risk assessment for sleep apnea. Increasingly, a cardiac intervention will be proposed for loss of function in daily activities, and objective means of assessing cardiac function will be needed to ascertain whether the cause is cardiac or onset of dementia. In the normal population, the onset of dementia is heralded by a change in memory, whereas in Down syndrome it is often a change in behavior [63]. Once an interventional procedure or surgery is planned, steps must be taken for induction and emergence, with care-givers available and involved.

**Psychological issues**

As anesthesiologists, we meet patients in the circumstance of a change in health status. The change may be for an elective and anticipated intervention or cardiac surgery for which the patient is prepared; however, increasingly, we are meeting patients for non-cardiac surgery, pregnancy-related procedures, and for transesophageal echocardiography (TEE) and possible cardioversion for new onset of atrial arrhythmias in a previously asymptomatic patient. The anticipation of the surgical procedure, with the goal of improving functional status and quality of life, will be a very different experience from that of a young adult admitted with sudden onset of atrial arrhythmias, loss of functional capacity and the disappointment of learning of a change in their lifestyle and limitations. As outlined in the introduction, many adult patients with CHD are lost to follow-up because they feel well, and perceive themselves as being a normal person who had heart problems in childhood that were “fixed.” Many patients will have parents in attendance who are well versed in the history of their adult child’s health, and may have difficulty taking a secondary supportive role in decision-making. This is particularly true if there is a spouse that is, naturally, designated as the substitute decision-maker for the patient, should they encounter a prolonged length of stay in the cardiovascular ICU. Sensitivity to these issues, while empowering the ACHD patient, is an important consideration in discussing high-risk procedures.

There is a wealth of literature addressing the psychological well-being, quality of life, and life satisfaction of adults living with CHD [64–67]. Many of these studies are inconsistent in inclusion and exclusion criteria, but there are many reports from both the developed and developing worlds. ACHD patients have a reduced quality of life if measured in terms of functional capacity. When quality of life is measured in relation to psychosocial, occupational, and environmental aspects, they are as happy as, or happier than, the general public [66]. Another study found that ACHD patients were more resilient than the general population [64]. Interestingly, quality of life does not correlate to CHD subtype, cyanosis, personal resources, or family environment [68]. These studies are done in an outpatient setting and not in the context of a hospital admission with a change in health status. One in four ACHD patients will die of heart failure. Diminished quality of life in patients with heart failure correlates with female sex and younger age, and it seems reasonable to experience depression and frustration at not being able to do activities [68]. As more ACHD patients present for transplant or palliation, this will need to be addressed by ACHD multidisciplinary teams.

As a member of a multidisciplinary team, it is very important that the anesthesiologist-intensivist ensures that the patient has a clear understanding of the anesthetic risks and the implications for their quality of life, in addition to having realistic expectations of how the intervention will improve their activities of daily living and exercise tolerance, and over what time frame. Frank and explicit discussion of the role of the substitute decision in the presence of the patient and the substitute decision-maker should ideally occur in advance of the procedure, with an opportunity to review questions should they arise before the morning of the intervention or surgery. At times, psychological counseling may be offered to help the patient through this process, and support them in communicating their wishes for limits of care to their families.

**Cardiac lesions**

All of the lesions in this section are discussed in detail in individual chapters. There will be a brief discussion of the anesthetic issues that are unique to the adult for each of these lesions. ASDs, levo-transposition of the great arteries (L-TGA), and Ebstein’s anomaly are well known to present in the adult. Bicuspid aortic valve and the associated aortopathies are managed in adult practices independent of referral ACHD centers and will not be described here.
Atrial septal defect and partial anomalous venous connection

Patent foramen ovale

The foramen ovale is an essential component of the fetal circulation. Normally at the time of birth there is an abrupt reversal of the inter-atrial pressure gradient, allowing functional closure of the foramen ovale. Anatomic closure occurs during infancy in most of the population, but in up to 25% of the normal population closure is incomplete, and a potential inter-atrial communication exists into adulthood.

In normal adult physiological condition, left atrial pressure exceeds right atrial pressure, and the patent foramen ovale (PFO) “flap” is pushed closed. However, certain actions, such as release of a Valsalva maneuver, can cause transient reversal of the pressure gradient, allowing opening of the PFO and right-to-left shunting of blood. This may result in hypoxemia or paradoxical embolus. In the dynamic perioperative setting, alteration in the inter-atrial pressure gradient may occur due to variation in loading conditions and predispose to these events. Therefore, accurate diagnosis is important for risk stratification and management planning for the previously unrecognized PFO.

Diagnosis of PFO during TEE can be challenging, as the potential communication may exist without visualization of trans-septal flow with color flow Doppler. A contrast study (agitated normal saline injection, or agitated blood: saline in a 1:10 ratio) may be used to increase the sensitivity of TEE, with the contrast medium injected during Valsalva maneuver, which is released when contrast is visualized within the right atrium in order to maximally exploit the reversal of inter-atrial pressure gradients. Sensitivity of the test may be further increased by injecting via a lower body vein, as the Eustachian valve preferentially directs blood from the inferior vena cava (IVC) towards the inter-atrial septum.

PFO closure

Cardiac surgery

In the patient presenting for cardiac surgery who has an incidental finding of PFO, the decision to close or not is difficult, balancing the potential for shunt reversal against the possible additional risk of a change in the surgical plan. For those PFOs diagnosed intraoperatively, there will likely be no opportunity to discuss the matter with the patient or their substitute decision-maker. There are several settings in which intraoperative closure of the PFO is almost mandatory [69], namely right-sided open heart surgery on the beating heart, and those clinical scenarios in which altered loading conditions are very likely to produce a significant right-to-left shunt postoperatively, including heart transplantation, where right atrial pressure is expected to increase significantly, and implantation of a left ventricular assist device, which will produce considerable offloading of the left heart. In cases where bicaval cannulation and aatriotomy were already part of the surgical plan, most surgeons will elect to close an incidental PFO, as very little deviation from the original approach is required. In other scenarios, the decision as to how to proceed with an incidentally diagnosed PFO is more difficult. There are no prospective data available to guide the decision. A single, large, single-center retrospective study of patients undergoing cardiac surgery found that surgical closure of incidental PFO diagnosed at intraoperative TEE was associated with increased incidence of postoperative stroke [70]. However, due to the retrospective nature of the study, and the fact that patients undergoing mitral surgery were included in the analysis, it is difficult to extrapolate the results to those patients not requiring bicaval cannulation and aatriotomy. Individual and institutional practices vary widely, and there is no firm consensus on the best approach [71].

Cryptogenic stroke

In patients with cryptogenic stroke, the decision about whether to close a PFO or not is a controversial one. To date, three randomized studies have attempted to address this question, and none has shown any statistically significant risk reduction for mortality or embolic events for PFO closure over medical therapy [72–74]. However, each trial has shown a statistically insignificant trend towards benefit with closure. The Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment (RESPECT) trial also demonstrated superiority of closure in preventing embolic events or death in patient subgroups with substantial shunt or atrial septal aneurysm, and in their as-treated analysis for all patients [75].

Atrial septal defects

Atrial septal defect is one of the most common forms of CHD, representing 7% of CHD in childhood and 30–40% in adulthood [76,77]. ASDs may be further classified into four types of defect. These are well described in Chapter 21, but warrant discussion as ASD is one of the lesions that commonly presents in adulthood. The secundum ASD is the most common type of defect, representing 75% of ASDs. It may be associated with mitral valve prolapse. Ostium primum type ASDs are considerably less common, comprising 15% of cases. They are to be considered a form of AV canal defect, and may be associated with a cleft anterior mitral valve leaflet or, less commonly, a cleft in the septal leaflet of the tricuspid valve. The sinus venosus type represents 10% of ASDs. The superior vena cava (SVC) type of sinus venosus ASD is considerably more common than the IVC type, and both types are associated with partial anomalous pulmonary venous drainage. Coronary sinus type ASD is very rare, and results from unroofing of the coronary sinus into the left atrium (LA), such that blood may drain from the LA to the RA via the coronary sinus. It is important to identify an associated left-sided SVC, because of the risk of inadvertent systemic delivery of retrograde cardioplegia, and the possibility...
of a relatively small SVC and its implications for bicaval cannulation.

The amount of inter-atrial shunting depends on the interplay among the size of the defect, the relative compliance of the left and right ventricles, and the relationship between the resistances of systemic and pulmonary circulations. Larger left-to-right shunts lead to chronic volume overload of the right heart, with dilation of the RA, RV and PA. The flow pattern across the ASD is typically biphasic; although predominately left to right, there may be a period of brief reversal of flow in early systole and mid-diastole. This right-to-left flow may be increased in conditions of increased RA venous return or RA pressure, or decreased LA venous return or LA pressure [78,79]. Patients with larger uncorrected defects with significant long-standing high pulmonary blood flow may develop a degree of pulmonary hypertension. Severe pulmonary hypertension and the subsequent development of Eisenmenger syndrome are rare; if they do occur, they are likely due to simultaneous primary pulmonary hypertension [14]. Chronic right-sided volume overload may lead to the development of atrial arrhythmias, most commonly atrial fibrillation and flutter. These may be responsible for the first presentation of the adult patient with undiagnosed ASD [80]. Even patients with predominant left-to-right shunt are at risk of paradoxical embolism, due to transient elevations in RA pressure, previously mentioned, that lead to flow reversal. Patients at risk are younger and have smaller defects [81].

Atrial septal defect closure aims to prevent development of long-term complications. If surgical correction occurs before 5 years of age, there are no long-term consequences, whereas uncorrected defects in patients > 40 years of age are associated with an increase in mortality of 6% per year [77]. American College of Cardiology/American Heart Association guideline indications for ASD closure include right atrial or ventricular enlargement, paradoxical embolism, or documented orthodeoxia-platypnea (hypoxia and dyspnea while upright) [82]. In patients with pulmonary hypertension and net left-to-right shunting, ASD closure should be considered if PA pressures or PVR are less than two-thirds systemic, or with a positive response to pulmonary vasodilators or test occlusion [82]. The only absolute contraindication to ASD closure is a patient with severe irreversible pulmonary hypertension and no evidence of left-to-right shunt. Small ASDs (diameter < 5mm) with no evidence of RV volume overload do not need closure, unless associated with paradoxical embolism. Secundum ASDs are amenable to percutaneous closure using a catheter technique, whereas primum, sinus venosus, and coronary sinus defects require surgical closure. Features of a secundum ASD that suggest suitability for catheter intervention include smaller defects (<20mm) (although defects as large as 38mm have been successfully closed percutaneously), and an adequate septal rim (at least 5mm of septal tissue from the ASD to surrounding structures, including venae cavae, right-sided pulmonary veins, coronary sinus and AV valves) [83]. Left ventricular failure is increasingly recognized as a potential acute complication following ASD closure, particularly in elderly patients. ASDs cause not only chronic right heart volume overload, but also chronic under-filling of the left heart. In some patients, particularly those with pre-existing diastolic dysfunction, sudden volume loading of the left ventricle (LV) by closing a hemodynamically significant ASD may lead to the development of pulmonary congestion and overt LV failure [84].

**Partial anomalous pulmonary venous connection**

Partial anomalous pulmonary venous connection (PAPVC) refers to anomalous drainage of one or more pulmonary veins into the systemic venous circulation. The right-sided veins are involved in over 90% of cases. Most commonly, the abnormal connection is to the SVC or right atrium; however, the IVC, innominate vein, or coronary sinus may be involved. PAPVC occurs in 0.4–0.7% of patients at autopsy [85,86]. The vast majority of patients have associated lesions, particularly ASDs, with an associated sinus venosus defect occurring in 80%.

Pulmonary venous drainage results in a left-to-right shunt. This will be exacerbated by the presence of a concomitant ASD. Although in an anatomically normal circulation each pulmonary vein provides around 25% of the total pulmonary venous drainage, anomalous veins tend to contribute more than their expected proportion to the shunt flow, due to preferential drainage into the lower-pressure right atrium. Chronic right-sided volume overload may lead to pulmonary hypertension, which is more common in patients with two veins with anomalous return or other associated condition, such as ASD [87].

Surgical correction aims to redirect the anomalous pulmonary venous return to the LA, either by direct reimplantation or through the formation of baffles or conduits. Common complications following surgical repair include sinus node dysfunction, either due to direct injury or disruption of blood supply, and obstruction of venous pathways.

Scimitar syndrome is a rare anomaly, accounting for 3–6% of PAPVC. It consists of right-sided anomalous pulmonary venous drainage into the IVC around the level of the diaphragm. It is commonly associated with other anomalies such as right lung hypoplasia, right lung systemic arterial supply, dextrocardia, and bronchial anomalies [88]. It is named after the appearance of the anomalous vein on chest X-ray, the convex course of which resembles the Turkish sword of the same name [89]. Surgical repair of scimitar syndrome is complex, and frequently requires deep hypothermic circulatory arrest to facilitate redirection of the anomalous pulmonary vein to the LA by direct reimplantation or baffle formation. Postoperative complications are not uncommon, and thrombosis of the anastomosis may be life-threatening and require urgent lobectomy or pneumonectomy [89].
KEY POINTS: ATRIAL SEPTAL DEFECT AND PAPVC

- PFO should be closed if symptomatic, and during the course of surgery for other defects.
- Secundum ASD is the most common type; pulmonary vascular disease is rare and usually does not manifest until 40 years of age or older.
- PAPVC is commonly associated with sinus venosus ASD and must be repaired by patch-baffle at the time of ASD surgery.

Ventricular septal defect

Ventricular septal defect is the most common congenital cardiac lesion in the adult population, excluding bicuspid aortic valve, with a prevalence of 0.3 per 1,000, and representing around 10% of ACHD [90]. The anatomical considerations and classification of VSDs are described in detail in Chapter 21. Briefly, membranous defects, located in the membranous septum, are associated with TOF and abnormalities of the septal leaflet of the tricuspid valve. They are the most common defects (70%). Inlet VSD is located between the mitral and tricuspid valves, and represents a form of endocardial cushion defect, and as such may be associated with primum ASD and cleft mitral valve. Outlet, supracristal, or infundibular lesions are located just below the semilunar valves, and are associated with prolapse of the right coronary cusp of the aortic valve and aortic insufficiency. Muscular VSDs may be congenital or acquired, single or multiple, and small defects frequently close spontaneously in childhood.

The hemodynamic significance of a VSD is determined by several factors: size of the defect, the pressure gradient across the VSD, and the PVR. An isolated VSD will initially facilitate left-to-right shunting, which, in those VSDs with higher shunt volumes, will significantly increase pulmonary blood flow. Over time, this increased flow may result in changes in the pulmonary vasculature, which may lead to elevations of PVR, and eventually shunt reversal and Eisenmenger physiology. The anesthetic considerations for these various hemodynamic concerns are discussed in Chapters 21 and 28. The risk of endocarditis for all patients is not insignificant, even those with small defects, and patients should receive prophylaxis according to current guidelines [82].

Outside of the developing world, most patients who reach adulthood with unrepaired VSDs have small lesions of little hemodynamic significance. Indications for repair of these lesions include Qp:Qs > 1.5–2.1, evidence of LV volume overload, evidence of elevated PVR, or abnormalities of surrounding structures (such as aortic regurgitation in outlet or infundibular VSD). Surgical correction is contraindicated if Qp:Qs is < 0.7:1. Correction of the defect has traditionally been performed surgically; however, increasingly, catheter-based techniques are being used, facilitated by echocardiographic (either transesophageal or intracardiac) and radiological guidance, but long-term outcome data are lacking. Transient conduction defects, including complete heart block and bundle branch blocks, have been observed, as well as placement failure and impingement on the tricuspid valve [91]. Surgical correction traditionally occurs via a right ventricular approach and, as such, conduction disturbances are common postoperatively. Multiple “Swiss cheese”-type muscular VSDs may be technically difficult repair, and present for PA banding instead.

Patent ductus arteriosus

A small PDA may present in adulthood for the first time with a left-to-right shunt, and subsequent LV volume overload, dilation, and failure. General principles relating to patients with left-to-right shunt should be applied, as discussed earlier. Eisenmenger syndrome may eventually develop, resulting in the disappearance of the classical “machinery” murmur, and differential clubbing and cyanosis of the lower limbs only [92].

Most cases of PDA are amenable to percutaneous closure. If associated with other lesions requiring sternotomy, the PDA will be directly ligated. If pulmonary hypertension is present and has reduced the gradient between the aorta and PA to < 60mmHg, closure should only occur if the pulmonary hypertension is reversible [76].

Coarctation of the aorta

Aortic coarctation is frequently associated with bicuspid aortic valve, PDA, and mitral valve abnormalities. LV pressure overload results in concentric left ventricular hypertrophy and diastolic dysfunction. Arterial hypertension occurs in the upper limbs, with relative hypotension in the lower limbs. More severe coarctation may result in the development of collateral vessels to maintain distal perfusion. Long-standing hypertension results in accelerated coronary artery disease, risk of stroke, and aortic dissection. Although aortic coarctation is frequently stented or repaired in childhood, it may recur in adulthood. Aneurysm formation may also be a late complication of repair. Less commonly, a patient may present for the first time in adolescence with upper body hypertension.

Over the past decade, stenting has been increasingly used for both primary and recurrent coarctation. Guidelines suggest intervention when the gradient exceeds 20mmHg, or when proximal hypertension is explained by the narrowing, even if the gradient is < 20mmHg. Open repair may be required in some cases. The approach is usually via left thoracotomy, and requires lung isolation and collapse of the left lung. The presence of well-developed collaterals will prevent excessive proximal hypertension on clamping of the aorta. During the period of clamping, vasoconstrictors may be required to maintain downstream perfusion pressure. Postoperatively, hypertension is common, and may persist.
In pregnancy, it is essential to monitor systemic arterial blood pressure below the level of the coarctation as index of placental perfusion. With low thoracic or high lumbar epidural, distal pressure may drop significantly, whereas proximal pressures may not be affected.

**KEY POINTS: VENTRICULAR SEPTAL DEFECT, PDA, COARCTATION**

- Unrepaired VSDs in adults are usually small; in developing countries they may be large and accompanied by pulmonary vascular disease.
- PDA in adults is seen in developing countries and may be accompanied by Eisenmenger syndrome.
- Coarctation in adults is accompanied by hypertension, early atherosclerosis, and extensive collaterals.

**Pulmonary valve stenosis**

Pulmonary stenosis (PS) is a relatively common lesion, representing approximately 8–10% of all CHD. It may occur as an isolated phenomenon, in association with other defects such as ASD, VSD, or PDA, or as part of the constellation of features of TOF (see later). The stenosis is most commonly at the level of the valve, but may also be supravalvular or subvalvular. Valvular PS is associated with Noonan syndrome, as well as TOF and other cardiac lesions such as Ebstein’s anomaly and TGA. Subvalvular PS may occur as a primary phenomenon, as in TOF, or secondary to right ventricular hypertrophy in response to valvular or supravalvular PS. Supravalvular PS may occur in association with Noonan, DiGeorge and congenital rubella syndromes.

Although many patients with more severe lesions present and are treated in the neonatal period or early childhood, a proportion of patients with milder disease will remain asymptomatic until adulthood. In these patients, indications for intervention include right ventricular outflow tract (RVOT) gradient > 64 mmHg, symptomatic PS, decreased RV function, double-chambered RV (RV chamber divided in two by anomalous muscle bands), significant arrhythmias, or ASD or VSD with right-to-left shunting [93]. Balloon valvuloplasty is generally the first-line treatment of choice. Surgical repair may be required in patients with more complex anatomy, infravalvular stenosis, or additional associated defects. Open repair generally takes the form of open valvulotomy with or without transannular patch. Valve replacement is rarely required as first line treatment.

Patients who have previously had interventions for PS frequently present in adulthood with either recurrent stenosis or haemodynamically significant pulmonary regurgitation. Intervention is indicated in all cases of symptomatic pulmonary regurgitation, and should be considered if there is an objective decrease in exercise capacity, progressive RV dilatation, RV systolic dysfunction or tricuspid regurgitation, or sustained atrial or ventricular arrhythmias [93]. Traditionally, pulmonary valve replacement is performed via sternotomy, with homograft or bioprostheses favored over mechanical prostheses due to the risk of thrombosis in the pulmonary position. However, percutaneous pulmonary valve replacement is emerging as an alternative therapy, with promising early outcomes in selected patients with either native, prosthetic, or conduit re-stenosis or regurgitation [94,95]. However long-term data are lacking, and currently there are no available prostheses larger than 26 mm (a 29 mm SAPIEN (Edwards Lifesciences, Irvine, CA, USA)) valve is available in Europe[95]), limiting the application of this therapy in patients with pulmonary regurgitation and larger annuli. Early complications include coronary artery compression and conduit rupture.

**Ebstein’s anomaly**

Ebstein’s anomaly is a rare anomaly, occurring in 1–5 per 200,000 live births and accounting for less than 1% of all CHD [96]. It is characterized by apical displacement of the septal and posterior leaflets of the tricuspid valve (Figure 16.4). These leaflets may lack chordae and are therefore attached directly to the ventricular wall. This anatomic change results in tricuspid regurgitation, and atrialization and reduced functional size of the RV. The anterior leaflet of the tricuspid valve may be large and redundant, resulting in RVOT obstruction. Ebstein’s anomaly is frequently associated with other cardiac anomalies, particularly ASD. Secundum ASD occurs in over 90% of individuals. Pulmonary atresia may occur, due to reduced blood flow through the RVOT in utero.

Those with relatively milder disease may present for the first time in adulthood. It is one of the few congenital heart lesions that can present in adulthood, often with the new

Figure 16.4 A five-chamber view of severe Ebstein’s anomaly. Note the apical displacement of the septal leaflet. RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle; TV, tricuspid valve.
onset of atrial flutter. This presentation is often in the context of a surgical event, such as acute cholecystitis, appendicitis, or labor and delivery, when the patients have an unexpected physiologic stress. The degree of abnormality lies on a very broad spectrum of natural history and severity, depending on the degree of displacement of the tricuspid valve leaflets, and the degree of shunting across a PFO or secundum ASD. First presentation beyond the fifth decade is rare; however, patients may present as late as the eighth decade [97]. Older patients most commonly present with arrhythmias, but paradoxical embolus may occur in those with ASD or PFO.

Left ventricular dysfunction is increasingly recognized and is multifactorial in etiology. RV volume overload and geometrical alteration may impact on the left ventricular function. Chronic hypoxemia may lead to left ventricular subendocardial fibrosis. There appears to be an association with left ventricular non-compaction [98]. A variety of corrective procedures may be performed, which may involve repair or reimplantation of the tricuspid valve leaflets, plication of the atrialized LV and closure of inter-atrial communications. A concurrent anti-arrhythmia procedure, such as the Maze procedure, is frequently performed. Bioprosthetic tricuspid valve replacement may be required in some cases. A bidirectional Glenn shunt may be performed in some instances, particularly where it is anticipated that RV function will be inadequate following repair. In some patients with severely abnormal and dysfunctional RVs, a total cavopulmonary shunt may be indicated. Chapter 23 contains an extensive discussion of Ebstein’s anomaly and surgical approaches.

Tetralogy of Fallot

Tetralogy of Fallot is the most common repaired cyanotic defect in the ACHD population and these patients frequent the electrophysiology laboratory, urgent and emergent cardioversion lists, interventional suite for percutaneous valve and/or branch PA dilation and the operating room for pulmonary valve replacement, RVOT plication/remodeling and tricuspid valve repair/annuloplasty.

Rarely does an adult present for primary correction in the developed world. The majority of older adults will present for a re-intervention or surgery having had a palliative systemic-to-pulmonary artery shunt for cyanosis followed by a repair as a child. Younger adults were likely diagnosed in utero and had medical therapy in the first few weeks to months of life and subsequent correction at 3–6 months [99,100]. Most patients will have had a transannular patch to widen the RVOT at the time of repair, RVOT dilatation and eventually tricuspid regurgitation due to RV dilatation. A smaller percentage of adults will have restriction of their RVs, which correlates with having had a transannular patch, elevated troponins immediately after repair, and inotropic requirements and prolonged time in the ICU. Restriction appears to protect the RV from ventricular dilatation due to pulmonary insufficiency [99]. The optimal timing of a pulmonary valve replacement with or without an RV plication and/or a tricuspid valve annuloplasty has been difficult to define, but a consensus amongst reference centers is forming. Intervening prior to RV end-diastolic volumes of 170 mL/m² or end-systolic volumes of 85 mL/m², and prior to QRS duration reaching 180 milliseconds is suggestive of improving RV remodeling and reducing the risk of sustained ventricular tachycardia, atrial arrhythmias, and sudden death [99,101–104].

The burden of arrhythmias for adult tetralogy is substantial, both atrial and ventricular, along with a lifelong risk of sudden death. A recent multi-institutional cross-sectional study found at least one type of clinically sustained arrhythmia in 435/553 TOF patients > 18 years [105]. Atrial arrhythmias, flutter and fibrillation, correlate with tricuspid regurgitation and older age of repair. Ventricular arrhythmias and sudden death correlate with increased QRS duration and older age of repair. In a large multicenter study, there was no predictive value for frequency and complexity of ventricular ectopy on Holter monitor in predicting sudden death. In a large cohort of adults with tetralogy, six out of 793 experienced sudden death during the 10-year study period, and only one of the 16 patients had documented arrhythmias prior to their sudden death [102]. Assessment of RV function and mass by magnetic resonance is now the gold standard, and a multicenter registry of TOF adults has shown that RV hypertrophy, RV dysfunction and LV dysfunction as defined by magnetic resonance correlate with sustained ventricular tachycardia [106]. Symptomatic atrial arrhythmias, ventricular tachycardia, and catastrophic ventricular tachycardia/ventricular fibrillation are as important to the anesthesiologist as the hemodynamic considerations for TOF, and the adult cardiac anaesthesiologist will experience an increasing exposure to TOF patients for electrophysiological mapping, ablation, and insertion of prophylactic defibrillators.

Management of the adult TOF patient for pulmonary valve replacement with or without RV plication, tricuspid valve annuloplasty, or cryoablation is one of the most common surgical procedures in a referral center for ACHD surgery. The hemodynamic goals must focus on maintenance of RV contractility, minimizing PVR, and avoidance of arrhythmogenic triggers. Intravenous and inhalational agents must be chosen that will not diminish contractility, have minimal effects on the PVR, and minimal arrhythmogenic potential. Ventilation should be at or close to FRC, with minimal positive end-expiratory pressure (PEEP), and converted to a spontaneous mode of ventilation when possible once in the postoperative or ICU setting. Along with recognition of the detrimental effects of long-term pulmonary insufficiency and RV dilatation due to transannular incisions, adult anesthesiologists will see an increasing number of young adults with residual stenosis and outflow tract obstruction for both the operating room and catheterization laboratory. It is anticipated that these patients may be better candidates for
percutaneous valves as adults with RVOTs of reasonable dimensions. These are described in the section on PS. Anticipation of, and a treatment plan for, both atrial and ventricular arrhythmias is essential [107].

Adults who are unrepaired frequently come from developing nations and have an anatomy favorable to surviving as an adult. They will have all the anesthetic considerations of living with cyanotic heart disease, as well as the co-morbidities described previously in this chapter. The anesthetic management of an unrepaired TOF patient for definitive repair is described in Chapter 23 and there are a few special considerations for the adult patients. Patients who survive will likely have aortopulmonary collaterals that can be problematic in the operating room and for postoperative ICU management. Preoperative coil embolization of large collaterals will reduce the run-off of aortopulmonary collaterals, which will lower MAP on bypass. The pulmonary vasculature may not be well developed and patients will have less lung reserve. Postoperatively, the pulmonary vasculature will have a full cardiac output as well as additional left-to-right shunting from pulmonary collaterals, and there will be a risk of life-threatening pulmonary hemorrhage, which may require lung isolation and definitive management in the interventional suite and/or operating room.

KEY POINTS: PULMONARY STENOSIS, EBSTEIN’S ANOMALY, AND TOF

- PS is common and may be asymptomatic until adulthood when right heart failure occurs.
- Ebstein’s anomaly may present for the first time in adulthood; atrial arrhythmias are frequently the first presenting sign.
- TOF is the most common ACHD repaired cyanotic defect; pulmonary valve replacement and arrhythmia treatment are common procedures.

Congenitally corrected transposition of the great arteries

Levo-transposition of the great arteries (L-TGA) is also called congenitally corrected transposition of the great arteries (ccTGA), and this is also called congenitally corrected or L-transposition of the great vessels, terms that confuse many. The term implies that the patients are “born corrected.” These patients have both AV discordance and ventriculoatrial (VA) discordance; the RA is connected to a morphological LV that is subpulmonic; the LA is connected to a morphological RV which is subaortic. It is one of the few congenital heart defects that presents in adults and may be misread on echocardiography as a normal four-chamber heart (the tricuspid valve is more apically placed.)

The majority of these patients have an Ebstein-like malformation of the tricuspid, systemic AV valve, with moderate to severe systemic AV valve regurgitation, and less commonly septal defects and PS [108,109]. In the absence of associated anomalies, these patients present in the second and third decades of life with systemic AV valve regurgitation and symptoms of heart failure. Arrhythmia is a common presentation, including complete heart block with increasing age, as well as atrial arrhythmias, usually as a symptom or consequence of a greater problem such as a failing systemic ventricle with tricuspid regurgitation. Much like the Mustard and Senning patients (see later) they are managed like a patient with dilated cardiomyopathy and likely have a degree of pulmonary hypertension.

Surgical interventions depend largely on the associated anomalies. The patients with PS have subpulmonic LVs that are primed or trained for systemic pressures, and may be candidates for an atrial and arterial “double switch” [110]. Patients without subpulmonic obstruction can be considered for sequential PA banding to train the LV for a potential “double switch.” This requires multiple surgical interventions, and many patients have improvement with the PA band alone, which causes a septal shift due to increased left ventricular pressures and improvement in the systemic RV geometry with less tricuspid regurgitation [111]. This may be a destination on its own or the patient can proceed to a combined Mustard/Senning with either an arterial switch or a Rastelli procedure [111]. Additional details about surgical approaches to corrected transposition are presented in Chapter 24.

Dextro-transposition of the great arteries

Levo-transposition of the great arteries (L-TGA) is also called congenitally corrected transposition of the great arteries (ccTGA), and this is also called congenitally corrected or L-transposition of the great vessels, terms that confuse many. The term implies that the patients are “born corrected.” These patients have both AV discordance and ventriculoatrial (VA) discordance; the RA is connected to a morphological LV that is subpulmonic; the LA is connected to a morphological RV which is subaortic. It is one of the few congenital heart defects that presents in adults and may be misread on echocardiography as a normal four-chamber heart (the tricuspid valve is more apically placed.)

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The morphologic right ventricle acts as the systemic ventricle. Although rarely done now, there are many adults living with atrial baffle repairs, which redirect the atrial blood to the opposite ventricle. (Figures 16.6 and 16.7). The Senning and Mustard operations were the standard of care, often with a prior temporizing systemic-to-pulmonary artery shunt, until the mid-1980s when the arterial switch became the preferred method. Retrospective reviews reveal reasonable quality of life until the fourth decade with 25-year survival rates of 91% (Senning) and a 76% (Mustard) [112]. The RV remains as the systemic ventricle. Patients with a Mustard or Senning repair frequently have baffle leaks, obstruction or narrowing of the SVC, IVC or pulmonary veins, sinus atrial arrhythmias, sick sinus syndrome, and inevitably systemic ventricular failure with systemic (tricuspid valve) AV valve regurgitation [109,113].

The anatomy can appear complicated; however, there is a physiological correction and a red cell will traverse the cardiopulmonary circulation in an appropriate sequence but with reversed roles of the ventricles. Central venous access can be challenging, as the catheters may get caught up in the baffle or make an abrupt turn from the LV back to the PA. The patients are frequently pacemaker-dependent with multiple central vein manipulations in the past and narrowed SVC. Hemodynamically they are much like managing a dilated cardiomyopathy, often with pulmonary hypertension due a failing systemic ventricle with AV valve regurgitation. Agents to promote contractility and systemic afterload reduction are the goals.

Case reports of PA banding in adults to train the subpulmonic LV for systemic pressure and subsequent take-down of the Mustard baffle and arterial switch had mixed success, with significant mortality and morbidity [114]. Patients may present as an adult for revision of a baffle; however, they are far more frequently scheduled for pacemaker, defibrillator, and electrophysiology procedures. Cardiac transplantation is frequently not offered to these patients, due to complicated anatomical considerations requiring a “no lung” donor, and pulmonary hypertension.

D-TGA with an arterial switch
In the late 1970s and early in the 1980s, CHD pediatric centers moved from the Senning and Mustard repairs to the Jatene or arterial switch operation [115]. These patients have yet to reach adult centers in large numbers, but complications include coronary artery perfusion defects and aneurysms of the neo-aortic root. The advantage is that the LV is the systemic ventricle: AV and VA synchrony is restored.

D-TGA with VSD and PS and a Rastelli repair
Patients with D-TGA (AV concordance and VA discordance) having a VSD and PS are corrected in childhood with a Rastelli repair, which entails a tunnel from the LV through the VSD to the aorta, and an extracardiac conduit that connects the RV to the main PA. The LV is restored as the systemic ventricle; however, these patients return for obstruction of their conduits. In the past these were surgical cases with considerable risk of entry into the conduit on sternal entry, but increasingly these patients are dealt with in the interventional suite for valve-in-valve pulmonary valve replacement and balloon dilatation of the conduit. Freedom from death or transplant is disappointing in this
There is no access to the atria and ventricle with a central tunnel Fontan or a total cavopulmonary connection is that an anesthesiologist involved in the resuscitation of lateral ablation, and, in some cases, transplant. The challenge for internal cardiac defibrillators (AICDs), mapping and cardioversion, epicardial pacemakers, and automatic defibrillators will continue to rise and patients will present for cardioversion, electrophysiological mapping and ablation, and arrhythmia surgery in conjunction with conversion to a cavopulmonary connection [124]. There are several case series of successful conversion from conventional RA to PA connection to a cavopulmonary connection with concomitant arrhythmia surgery, with many of the studies having patients with a median age of the late teens and early adulthood [125,126]. The goal is to improve the hemodynamics and loss of energy in the blood flowing into the PA, and to prevent atrial dilatation and subsequent arrhythmias. Whether this lessens the burden of atrial arrhythmias and sudden death in later decades remains to be seen, as this population has had follow-up for 10–15 years, and although 85% are free from supraventricular tachycardia recurrence, they have not been followed as long as the previous version of the Fontan procedure [124].

A large follow-up cohort in Boston found no difference in long-term survival between RA to PA connection Fontans and total cavopulmonary connections [119].

Fontan patients have no “pump” for systemic venous return to get to the LA. For successful management they must have adequate right-sided filling pressures, low PVR, unobstructed pulmonary vein inflow to the LA, AV synchrony, a competent systemic AV valve with laminar inflow, no outflow tract obstruction, and afterload reduction for the systemic ventricle. Patients may have had a fenestration from the Fontan connection to the systemic or common atrium, and precautions for venous emboli to the systemic circulation will be needed. Surgical and anesthetic techniques must be chosen that keep all of these goals in mind, but also the planning of the postoperative recovery and step-down must take them into account. Conversion to the spontaneous breathing mode of ventilation and early extubation are the goals.

The burden of arrhythmias in this population will continue to rise and patients will present for cardioversion, electrophysiological mapping and ablation, and arrhythmia surgery in conjunction with conversion to a cavopulmonary connection [124]. Patients with lateral tunnel Fontans and cavopulmonary connections will have limited or no access to the atria and ventricles. Transconduit/baffle mapping is possible with radiofrequency transcatheter techniques [113]. Fenestrations to the atrium from the lateral tunnel or the conduit of the cavopulmonary connection are a restricted window for the electrophysiologist, akin to painting an interior room of a house through a small window in an exterior wall while standing on a ladder. The procedures are lengthy for both the anesthesiologist and the patient, as the patient must not be too heavily sedated so that the electrophysiological physician can map the arrhythmia,
and yet should be comfortable to remain still for several hours. Cardioversions are fraught with complications, as there is no possibility of placing a temporary pacing wire in the event of conversion to a bradycardia, and resuscitation drugs must traverse the pulmonary vasculature in the situation of manual positive pressure ventilation and hemodynamic collapse. An experienced adult cardiac anesthesiologist will have large-bore intravenous access and a clear plan (and a backup plan) for each cardioversion. Ideally, cardioversion should occur in a central location in the hospital where ancillary personnel can be quickly recruited for assistance and supervised directly by senior staff.

**Figure 16.8** Fontan procedure modifications. (A) The original Fontan Operation (right atrial to pulmonary artery connection); (B) the lateral tunnel modification; (C) extracardiac cavopulmonary connection. RPA, right pulmonary artery; SVC, superior vena cava; RA, right atrium; IVC, inferior vena cava; ASD, atrial septal defect. Reproduced with permission from reference 123: d’Udekem Y, Iyengar AJ, Cochrane AD, et al. The Fontan procedure: contemporary techniques have improved long-term outcomes. Circulation. 2007;116:I157–64.

**KEY POINTS: SINGLE-VENTRICLE/FONTAN ANATOMY**

- Early Fontan connections involved direct RA to PA anastomosis; right heart failure and arrhythmias necessitate conversion to lateral tunnel or extracardiac connections in some adults.
- Treatment of HLHS with the Fontan operation since the 1980s has created a growing population of young adults with failure of the systemic RV.
- Avoidance of prolonged positive pressure ventilation and hypovolemia are important anesthetic considerations.
- Arrhythmia procedures, including electrophysiological mapping/ablation, pacemakers, and cardioversion are common in the adult Fontan and require careful planning and provision for backup during emergencies.

**Transplant and the ACHD patient**

Adults with CHD comprised only 2% of the heart transplants reported to the United Network for Organ Sharing in the United States from 1987 to 2006 [127]. These patients (689/35,334) spent a longer time on the waiting list, were more likely to have PVR exceeding 4 Wood units, and, once they did proceed to heart transplant, to have longer ischemic times and a higher 30-day mortality (16% with ACHD vs. 6% with acquired heart disease). Interestingly, once these patients survive the immediate 30-day period, they have comparable 5- and 10-year survival [127]. Another study examining CHD patients also utilized the United Network for Organ Sharing in the United States from 1993 to 2002 and included pediatric, teen and adult recipients with a mean age of 14.2 years. Risk factors for early mortality included older recipient age (risk ratio [RR] = 1.5), previous Fontan (RR = 8.6), longer ischemic time (RR = 1.6), interaction of donor and recipient ischemic time (RR = 1.4) and a higher pre-transplant RA pressure (excluding Fontans, RR = 2.4). The 5-year survival in the Fontan patients was 60%, and was 74% in the non-Fontan patients [128]. A case series report of cardiac transplantation after the Glenn or Fontan procedure found the 30-day mortality of single-ventricle transplants to be very high (28%) and yet those that survive the initial postoperative period have favourable 1-year (71.5%) and 5-year (67.5%) survival [129].

The competition for scarce resources with acquired heart failure patients will make transplant as a destination unlikely for most of this population. Many of the patients will have exclusions that will prohibit them for consideration for heart transplant, and, if listed, will spend a longer time waiting for a “non-lung” donor due to the requirement of increased length of donor vessels [38].
When a complex CHD patient is scheduled for a transplant, it is very important for the anesthesiologist to be involved in the surgical planning process, as vascular access and anesthetic induction must be timed appropriately, often with all lines inserted with conscious sedation, so that ischemic time of the donor heart is not increased for anesthetic or surgical reasons.

Although many ACHD patients may be candidates for transplant, most will not be listed and the anesthesiologist’s involvement will increasingly be for procedures to reduce the morbidity of arrhythmias, cardioversions and AICD implants, and non-cardiac surgery.

Non-cardiac surgery in the adult with CHD

Non-cardiac surgeons will increasingly have referrals of patients with ACHD, which will be independent of the surgical complaint. The evidence of a cardiac lesion may be found on the review of systems, or at the time of physical exam with the discovery of sternalotomy or thoracotomy scars. Patients may be surprised or evasive when questioned about their cardiac past, will frequently describe their lesions in simplistic terms (“I had a hole in my heart”), and may be reluctant to pursue cardiac follow-up or investigations. Like other non-cardiac patients, they want to have a consultation completed and to return to their ordinary life as soon as possible. The increasing number of adults living past 18 years will mandate that many non-cardiac procedures will not occur in specialized tertiary care centers. Although the Bethesda and Canadian Consensus conferences outlined goals for care of the ACHD patient in North America, these centers have not materialized [1,130,131]. Patients will want to explore care in their immediate community for convenience and, in the case of US patients, insurance. The challenges for the next decade are the increasing complexity of these patients, and the organization of their care for elective, urgent, and emergent non-cardiac procedures.

Frequently, a surgeon in a community setting, whether it is a large referral hospital or a regional community hospital, is an ACHD patient’s first contact with a medical practitioner in the period since discharge from a pediatric setting. A large population of 22,096 ACHD patients living in Quebec and > 18 years old in 1996 were divided into two groups, severe and other, based on anatomic diagnosis, and followed for the 5 years from 1996 to 2000. Hospital utilization rates were examined: 91% had a general practitioner and the mean number of visits over the 5-year period was 15; the mean number of specialist outpatient visits (including surgeons) was 10 visits over a 5-year period, and this exceeded the number of outpatient cardiology visits by 250% [132]. One conclusion is that the patients bypass cardiology and seek out specialist care independent of their cardiologist’s input.

Cardiac anesthesiologists, cardiologists, and intensivists have a special understanding of the ACHD patient and their unique physiology. They must play a leadership role, providing care directly or advising colleagues in the community how best to provide care for these patients, and when it is necessary to transfer care. This expertise is not limited to the operating room, but should also be available in the preoperative optimization and planning, postoperative monitoring, and pain management. These specialties must function as an “outreach team” for this special population, and outline physiologic parameters and goals for the postoperative recovery [133–135]. Accessing the patient’s cardiology records is more challenging, but it is achievable, as increasingly all records are electronic and retrievable by the cardiologist or anesthesiologist on call at the referral center. Initiating a telephone consult and obtaining advice about preoperative optimization and operative management early in the presentation are advisable. Red flags for referral to a teaching center include:

- Cyanosis or a deterioration in oxygenation from baseline
- Pulmonary hypertension
- New onset of arrhythmia or difficult rate control in an established atrial arrhythmia
- Systemic hypotension in relation to the patient’s baseline
- Systemic ventricle dysfunction.

There are patient factors that will bias toward management at the tertiary referral center, as well as surgical factors that ordinarily are of minor concern, but a major issue in the patient with unrestricted shunts and PVR-dependent lesions. The advantages of a tertiary care hospital are that, should an event occur, there is much more latitude in the deployment of staff to assist in a hemodynamic or volume resuscitation.

Laparoscopic and video-assisted surgery is increasingly becoming the standard for patients in general surgical, gynecological, and urological operations. Thoracic surgery utilizes insufflation of air, as the chest wall is rigid, and CO₂ is not needed: PVR will rise with the atelectatic lung and hypoventilation during one lung ventilation, but not from absorption of insufflated PaCO₂. Although insufflation of CO₂ is in conflict with the physiologic goals intraoperatively, particularly for PVR-dependent patients, minimally invasive approaches bode well for their recovery postoperatively. Its use in unrestricted shunts is controversial. Patient positioning (prone, lateral, Trendelenburg, or reverse Trendelenburg) may exacerbate or alleviate this conflict. A clear plan with a threshold for conversion to an open procedure must be discussed ahead of time with the attending cardiologist, anesthesiologist, and surgical team. Although more challenging for the anesthesiologist, the patient will benefit from a closed procedure and avoid the complications of a large incision. Patients having had a minimally invasive procedure will have less intravenous opioids postoperatively and will be less likely to have chest splinting, atelectasis, and elevated PaCO₂. Intraoperative monitoring of arterial and right atrial (caval) filling pressures with frequent sampling of
arterial blood gases will be necessary when contemplating a laparoscopic approach. Compromises can be made with the insufflation pressure.

Head and neck and upper airway surgery with either a controlled airway or suspension laryngoscopies for glottic and subglottic complications of prolonged intubation are not unusual cases in ACHD patients. Unlike the discussion regarding laparoscopic vs. open, the surgeon and the anesthesiologists do not have much choice about technique and it is not the choice of anesthesia agents but the maintenance of physiologic goals that is the challenge. Spontaneous ventilation in a PVR-dependent patient eliminates the concerns of positive pressure ventilation impeding flow of blood from the cava and right to the left atrium. Laser laryngoscopy and bronchoscopy cases with jet ventilation on an FiO₂ < 0.30 will be difficult for Fontan and Glenn patients, patients with pulmonary hypertension, and those reliant on a balanced SVR and PVR with the potential to exacerbate shunting.

Major spine surgery in the prone position is a challenging case in ordinary circumstances and is frequently needed in ACHD patients for deteriorating lung function due to kyphoscoliosis and to prevent further worsening of the spinal deformity. In patients with adolescent idiopathic scoliosis, surgery via an anterior thoracic approach may result in initial worsening of lung function, when compared with surgery involving a posterior approach [136]. These findings may be extrapolated to the ACHD population. The prone position may result in a reduction in systemic venous return, related to lower limb dependent position. IVC compression should be identified and rectified, as it may compound this issue. Reverse Trendelenburg positioning may be required to reduce venous engorgement at the surgical site. Monitoring invasive arterial and central venous pressures is recommended; however, it should be noted that in the pediatric population, a lack of correlation between indicators of volume status by TEE and measured filling pressures has been demonstrated [137]. In larger, multi-level cases, considerable blood loss can occur, and appropriate blood conservation strategies should be initiated. These may include use of antifibrinolytic agents, use of autologous blood transfusion strategies, and intraoperative cell salvage. Hypotensive anaesthesia has been used safely in the normal adult population, but caution should be exercised in those ACHD patients to whom a significant reduction in SVR would be deleterious [138]. The one teaching hospital death in a large series of Eisenmenger syndrome adults for non-cardiac surgery was an in-patient who had come in for spinal instrumentation [139]. Patients are at increased risk of venous thromboembolic complications, related to prone positioning, long surgical times, and extended postoperative convalescent period. Mechanical prophylaxis with compression stockings and sequential pneumatic compression devices is mandatory. The hemorrhagic risks of pharmacological anticoagulation must be carefully considered, as major bleeding and epidural hematoma are devastating complications.

Many patients will be receiving ongoing monitoring and support in an established ACHD center; however, frequently a surgeon will be the patient’s first contact with a specialist physician in several years of having been lost to follow-up. Community anesthesiologists and surgeons are in a unique situation to identify a patient at risk and, in addition to pre-, intra-, and postoperative care, reconnect them to an ACHD team for subsequent care. The consultant ACHD anesthesiologist can facilitate the surgery and act as a resource for the non-cardiac anesthesiologist or act as a second consultant.

### KEY POINTS: NON-CARDIAC SURGERY

- Community surgeons will increasingly see referrals of ACHD patients who have not had appropriate cardiology follow-up.
- Cyanosis, pulmonary hypertension, new arrhythmia, and ventricular dysfunction necessitate referral to a center with experience in ACHD care and surgery.
- Laparoscopic and thoracoscopic surgery present many advantages to the ACHD patient and can be performed with adequate planning.
- Spine surgery is especially problematic due to blood loss and hemodynamic perturbations, and deserves special preparation in the ACHD patient.

### Conclusions

Resources for the anesthetic management of the ACHD patient for cardiac and non-cardiac interventions will increase over the next decade. Challenges include having personnel sufficiently trained to deal with this population, access to records and health histories, functional methods to enable transfer of care to a reference center when needed and an ACHD population better educated about their individual health. The proportion of the ACHD population living with heart failure in their third and fourth decades will increase and the anesthesiologist needed and an ACHD population better educated about their individual health. The proportion of the ACHD population living with heart failure in their third and fourth decades will increase and the anesthesiologist will be providing care for procedures that may not be cardiac surgery, but rather interventions that will include non-cardiac surgery or cardiology interventions for improving their quality of life. Congenital cardiac anesthesiologists must exhibit leadership in consulting and advising the adult cardiac anesthesiology community with regard to providing care for this rapidly expanding and complex population.

### Selected references

A full reference list for this chapter is available at: http://www.wiley.com/go/andropoulos/congenitalheart

cited paper that eloquently describes the increasing prevalence of adults with congenital heart disease. It is in the context of universal health care access in a county that has no private health care. It highlights the increasing age of those living with severe congenital heart disease.

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12 Alonso-Gonzalez R, Borgia F, Diller GP, et al. Abnormal lung function in adults with congenital heart disease: prevalence, relation to cardiac anatomy, and association with survival. Circulation 2013;127:882–90. The Brompton group examined the pulmonary function of 1,188 patients with ACHD followed in their program from 2000 to 2009. Thirty percent of the patients had moderately to severely impaired lung function. A reduced FVC was predictive of an early mortality and is correlated to the underlying heart defect, previous surgery, and the presence of scoliosis.

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132 Mackie AS, Pilote L, Ionescu-Ittu R, et al. Health care resource utilization in adults with congenital heart disease. Am J Cardiol 2007;99:839–43. A very good study utilizing the universal nature of Canadian single provider health care and how adults with CHD utilize health care. The denominator is comprehensive, in contrast to most studies where the reports are confined to the patients who show up to their clinic appointments. In the province of Quebec, 22,096 adults living with ACHD were followed during 1996–2000 and their utilization of health care was examined. Adults with CHD utilized health care significantly more than the general population at multiple levels of care.
Introduction: hemodynamic management following congenital heart surgery: a goal-directed approach

Guidelines delineate limits within which decisions can be made regarding the management of specific clinical problems; such guidelines improve outcome. A more prescriptive approach often takes the form of “goal-directed” therapy. Provided a relevant goal has been chosen and framed within a suitable evidence-based algorithm, goal-directed therapy has the potential to improve outcome, because treatment selection must be based on the “best practice” encapsulated within the protocol. The key to the success of any goal-directed therapy is the selection of the specific goal [1]. First, indicators used to achieve the desired therapeutic goal must be easy to obtain and safe, so, for example, invasive techniques may be judged to have an unfavorable risk/benefit ratio in children. Secondly, goals must be associated with an improved outcome; as such, the impact of an intervention on a surrogate physiological endpoint is insufficient evidence of clinical efficacy. It is likely that one of the greatest opportunities to improve patient outcomes comes not from discovering new treatments, but from using existing therapies more effectively.

A recent meta-analysis of randomized studies of adult patients [2] in various postoperative settings demonstrated a strong relationship between the duration and magnitude of oxygen debt and outcomes in high-risk surgical patients. There was a significant improvement in survival when pulmonary artery catheter goal-directed therapy was administered early or prophylactically (within 12–24 hours post-surgery or before organ failure occurred) to increase the cardiac index and oxygen delivery (DO₂). The aim of this goal-directed therapy is intervention before hemodynamic compromise or critical organ system compromise, because no amount of extra oxygen will rescue irreversible oxygen debt, organ failure, or cell death. Maintaining adequate tissue oxygenation, which is accomplished by optimizing oxygen transport balance, i.e. maintaining systemic DO₂ and minimizing oxygen consumption (VO₂), should prevent oxygen debt and improve outcome. This is probably the ultimate goal when treating children who have undergone surgery for congenital heart disease (CHD).
The VO$_2$/DO$_2$ balance following CHD surgery

A pathologic imbalance between VO$_2$ and DO$_2$ is thought to be the mechanism underlying anaerobic metabolism, multi-system organ failure, and death. The oxygen extraction rate (OER), calculated as

$$\text{OER} = \frac{\text{VO}_2}{\text{DO}_2} \quad (17.1)$$

might best reflect the oxygen consumption/delivery balance. The normal ratio of four to five times the amount of DO$_2$ to VO$_2$ suggests considerable reserve, and decreasing this factor (or increasing the OER) reflects less cardiovascular reserve. At high DO$_2$, VO$_2$ remains both stable and independent of oxygen supply. During periods of reduced DO$_2$, aerobic metabolism is maintained initially through increased oxygen extraction by the tissues. Through this mechanism, VO$_2$ remains independent of DO$_2$ until a critical OER is reached. At that point, which is generally thought to correspond to an OER between 0.5 and 0.6 [3], VO$_2$ becomes oxygen supply-dependent, and drops linearly to zero if the DO$_2$ further decreases. An OER above 0.5 has a positive predictive value of 74% for postoperative death in infants following CHD surgery [4]. The inflection point between the two slopes of the DO$_2$ curve indicates the critical level of DO$_2$. An illustration of these relationships is shown in Figure 17.1.

The relationship is altered further when VO$_2$ increases. When this happens, which is common in the postoperative period, the critical DO$_2$ also increases, as shown in Figure 17.1, meaning that a VO$_2$/DO$_2$ imbalance occurs at higher DO$_2$ levels. Therefore, it follows that the goal of postoperative management is to increase DO$_2$ to delay the point at which a VO$_2$/DO$_2$ imbalance may occur.

The Fick equation states that

$$\text{CO} = \frac{\text{VO}_2}{(\text{CaO}_2 - \text{CvO}_2)} \quad (17.2)$$

where CO is the cardiac output, and CaO$_2$ and CvO$_2$ are the oxygen content of arterial and venous blood, respectively. At steady state, on the basis of the law of mass conservation, oxygen consumption and delivery must be equal.

$$\text{VO}_2 = \text{DO}_2 \quad (17.3)$$

In the setting of CHD, DO$_2$ is a resultant of several factors.

In the absence of intracardiac shunting, CO is equivalent to the systemic output (Qs) and the pulmonary output (Qp).

$$\text{CO} = \text{Qs} = \text{Qp} \quad (17.4)$$

and systemic DO$_2$ is a linear function of CO and CaO$_2$:

$$\text{DO}_2 = \text{CO} \times \text{CaO}_2 \quad (17.5)$$

These indexes change slightly in patients with univentricular physiology, as described in the following [5,6].

After the first stage or Norwood palliation, the systemic and pulmonary circulations become parallel, and the single ventricle assumes both the systemic and the pulmonary output:

$$\text{CO} = \text{Qs} + \text{Qp} \quad (17.6)$$

If making the assumption that the pulmonary oxygen uptake equals VO$_2$, then one can write separately:

$$\text{Qs} = \frac{\text{VO}_2}{(\text{CaO}_2 - \text{CvO}_2)} \quad (17.7)$$

and

$$\text{Qp} = \frac{\text{VO}_2}{(\text{CpvO}_2 - \text{CaO}_2)} \quad (17.8)$$

where CpvO$_2$ is the pulmonary venous blood oxygen content. We can combine these equations as follows:

$$\text{DO}_2 = \frac{\text{CO} \times \text{CpvO}_2}{(1 + \text{Qp}/\text{Qs}) - 2/(\text{Qp}/\text{Qs})} \quad (17.9)$$

which shows that DO$_2$ is a complex function of CO, pulmonary venous oxygen content, VO$_2$, and Qp/Qs ratio [5].

Following the bidirectional Glenn anastomosis, the blood that normally drains into the right atrium (RA) from the superior vena cava (SVC) is redirected to the pulmonary artery, and forms a combined upper systemic and pulmonary circulation, which is in parallel with the lower systemic circulation. The overall cardiac output is a sum of the upper and lower systemic outputs:

$$\text{CO} = \text{Q}_{\text{SVC}} + \text{Q}_{\text{IVC}} \quad (17.10)$$

As Qp = Q$_{\text{SVC}}$, it follows that

$$\text{CO} = \text{Qp} + \text{Q}_{\text{IVC}} \quad (17.11)$$

On the other hand,

$$\text{VO}_2 = k \times \text{VO}_2 + (1 - k) \times \text{VO}_2 \quad (17.12)$$
states that the whole-body VO₂ is the sum of the upper body oxygen consumption \((k \times VO₂)\) and that of the lower body \(\left[ (1-k) \times VO₂ \right]\), where \(k\) is the fraction consumed by the upper body.

If making the assumption that oxygen uptake through the pulmonary circulation equals VO₂, then one can write separately:

\[
Q_{SVC} = \frac{(VO₂ \times k)}{(CpvO₂ - CaO₂)} = Qp \quad (17.13)
\]

and

\[
Q_{IVC} = \frac{(VO₂ \times (1-k))}{(CaO₂ - CvO₂)} \quad (17.14)
\]

We can combine these equations as follows:

\[
DO₂ = CO \times CpvO₂ - (1 + Q_{SVC}/Q_{IVC}) \times \frac{(1-k) \times VO₂}{Q_{SVC}/Q_{IVC}} \quad (17.15)
\]

which shows that DO₂ is a complex function of cardiac output, pulmonary venous blood oxygen content, lower body oxygen consumption and \(Q_{SVC}/Q_{IVC}\) ratio [6].

To resume, albeit in a majority of patients the postoperative DO₂ is a linear function of CO and CaO₂, there are cases where DO₂ is a complex function of several other factors. This will be reviewed by the end of this chapter.

Changes in systemic oxygen balance have been well documented in both adults and children undergoing surgery with cardiopulmonary bypass (CPB) [7–10], with VO₂ increasing and DO₂ decreasing within the first 8–12 hours postoperatively. Several mechanisms may explain this phenomenon.

**Mechanisms underlying increases in VO₂ following cardiac surgery**

Evidence suggests that 50% of the postoperative increase in VO₂ in adults is due to the inflammatory response after cardiac surgery, and that variations in VO₂ are strongly correlated with the circulating levels of endotoxin, tumor necrosis factor-alpha, and interleukin-6 (IL-6) concentrations [10]. Other factors that may also explain the postoperative increase in VO₂ are shown in Box 17.1. Alterations in pulmonary function following cardiac surgery result in increased work of spontaneous breathing, which may require the redistribution of up to 15–20% of CO away from other organs [11]. Additionally, even when sedation and neuromuscular blockade were maintained to obviate the confounding effects of spontaneous ventilation, movement, agitation, and pain on VO₂, Li et al. [9] demonstrated a mean 14.7% increase in VO₂ within 4 hours of CHD surgery. The main determinants of this increase were a younger age and an increase in central temperature, with an approximate 11% rise in VO₂ per degree increase in central temperature following hypothermic CPB [9]. Fever is indicative of a postoperative inflammatory response; therefore, inhibiting the inflammatory response should reduce the increase in VO₂. The VO₂/DO₂ imbalance may be even larger in children than in adults for several additional reasons. First, resting VO₂ is greater in young children. Secondly, deep hypothermia is more frequently used during pediatric cardiac operations, and active rewarming restores only 65% of the heat lost, with muscles and subcutaneous fat remaining hypothermic at the end of CPB [12]. Finally, strong biochemical and hormonal stress responses occur in young children following cardiac surgery, further increasing VO₂ [13]. Fortunately, increases in VO₂ are usually closely paralleled by changes in DO₂, and OER varies little in patients with stable cardiac function postoperatively [9].

**Box 17.1: Factors responsible for a postoperative increase in oxygen consumption**

- Catecholamines: endogenous and exogenous
- Systemic inflammatory response
- Fever
- Consciousness, pain, anxiety
- Spontaneous breathing
- Enteral nutrition

Source: Bronicki et al. [138]. Reproduced with permission of Lippincott, Williams & Wilkins.

**Mechanisms underlying reduced DO₂ following cardiac surgery**

Equation (17.5) shows that DO₂ decreases are a result of a reduction in CO, or a reduction in CaO₂. Equation (17.5) can be rewritten as:

\[
DO₂ = CO \times (\text{hemoglobin} \; [g/dL] \times 1.34 \times \text{SaO₂}) + PaO₂ \times 0.003 \quad (17.16)
\]

The main determinants of CaO₂ are the hemoglobin concentration and SaO₂. The ideal hemoglobin concentration and management of perioperative transfusions largely depend on age and on the underlying CHD, and will not be discussed further. On the other hand, hypoxemia following cardiac surgery is multifactorial. CPB and reperfusion result in an intense generalized inflammatory reaction and diffuse endothelial damage accompanied by an increased vascular permeability, both of which induce pulmonary injury. Alveolar and interstitial edema, which may or may not be clinically apparent, reduce dynamic lung compliance and increase the ventilation/perfusion mismatch [14]. A reduction in functional residual capacity (FRC) after anesthesia and thoracic surgery may result in atelectasis, which will make the hypoxia even worse.

Low cardiac output syndrome (LCOS) is a common complication following CHD surgery in infants. Wernovsky et al. reported that 25% of neonates with transposition of the great arteries, and who underwent an arterial switch operation, showed a decline in cardiac index to <2L/min/m², which typically occurred between 6 and 18 hours after surgery [15]. This fall in the cardiac index was associated with an increase in systemic vascular resistance (SVR) of approximately 25%, and an increase in pulmonary vascular resistance (PVR) of nearly 40% over baseline values. Similar findings were reported by
Hoffman et al. [16] in a mixed population with a median age of 3 months and in an experimental model in piglets [17]. Under ideal circumstances, increased afterload is accompanied by a compensatory increase in ventricular contractility, known as ventriculovascular coupling. Stocker et al. [17] demonstrated a lack of compensatory increase in ventricular contractility in piglets early after CPB, and showed that therapeutic interventions aimed at reducing afterload actually prevented a reduction in CO.

Inflammatory response and ischemia–reperfusion injury will invariably cause some degree of postoperative myocardial dysfunction. Evidence suggests that patients undergoing atrial septal defect closure with short CPB and cross-clamping durations suffer from left ventricle (LV) systolic dysfunction, with a decrease in end-systolic elastance by 40% (Figure 17.2); this occurs independently of the type of cardioplegia and age [18]. Myocardial dysfunction in neonates is even more pronounced; neonates

Figure 17.2 Left ventricular pressure–volume loops from infants and children with intact ventricular septum, undergoing cardiac operations with short bypass and cross-clamping durations. The end-systolic elastance decreased from 2.30 mmHg/mL before bypass (A), to 0.93 mmHg/mL after bypass (B), reflecting a deterioration in the systolic function. (Source: Chaturvedi et al. [18]. Reproduced with permission of Elsevier.)
are known to have a relatively fixed stroke volume, to be highly dependent on heart rate, and to have diminished myocardial reserve (Box 17.2).

**Box 17.2: Limitations of the cardiovascular reserve in neonates**
- Decreased contractile reserve
- Cardiomyocyte contains fewer and poorly organized proteins
- Immature sarcoplasmic reticulum
- Decreased myocardial compliance
- Increased circulatory demands due to greater oxygen consumption

Source: Bronicki et al. [138]. Reproduced with permission of Lippincott, Williams & Wilkins.

Cardiopulmonary bypass results in early dysfunction of the pulmonary endothelium and an increase in PVR [19]. Increased PVR can be particularly problematic in neonates, in whom PVR is already high, and in young infants with increased preoperative pulmonary blood flow. Right ventricular (RV) failure due to acute pulmonary hypertension (PHT) is often associated with LCOS and hypotension which, added to the increased RV pressure, reduces the RV coronary perfusion pressure and may further reduce RV contractility. Even transient pulmonary pressure overload may induce persistent RV failure.

Finally, LCOS may develop due to several specific reasons related to the underlying CHD and to the surgical procedure. Coronary perfusion may be decreased following a systemic–pulmonary anastomosis as seen following the Norwood procedure, and result in dysfunction of the single ventricle. Nearly 50% of patients undergoing repair of tetralogy of Fallot have isolated diastolic RV dysfunction [20], and may develop LCOS due to insufficient preload of the LV. High PVR results in dysfunction of the cavo pulmonary anastomosis following a bidirectional Glenn or a Fontan procedure, due to a decrease of the single-ventricle preload, and to LCOS.

**KEY POINTS: THE VO₂/DO₂ BALANCE FOLLOWING CHD SURGERY**
- Pathologic imbalance between VO₂ and DO₂ is the mechanism of anaerobic metabolism, multi-system organ failure, and death.
- VO₂ commonly increases after CHD surgery from inflammation, fever, pain, and stress response.
- DO₂ commonly decreases after CHD surgery from inflammation, pulmonary dysfunction, LCOS, bleeding and anemia.

**Improving postoperative oxygen transport balance: preventive and therapeutic interventions**

Preventive and therapeutic interventions include all of the factors described in the previous section. Sedation, analgesia, and treatment of hyperthermia lead to substantial decreases in postoperative VO₂ [9]. In critically ill patients, mechanical ventilation with muscle relaxation reduces VO₂ by more than 20%, and as well as stabilizing pulmonary gas exchange, it can preserve the limited DO₂ for other vital organs [11]. The postoperative management of the pulmonary injury due to cardiac surgery and CPB are described in Chapters 8 and 19. Blood transfusions cause a significant increase in DO₂; transfusion thresholds are specific to age and dependent upon the underlying CHD, and limitations are due to increases in blood viscosity and PVR. This section will focus on the pharmacological treatment of LCOS.

The prevention and early treatment of the LCOS are major priorities both intraoperatively and postoperatively. Evidence supporting preventive drug therapy for LCOS is derived primarily from the landmark PRIMACORP (Prophylactic Intravenous Use of Milrinone After Cardiac Operation in Pediatrics) study [16], which reported a 55% reduction in the risk of postoperative LCOS after administration of high-dose milrinone. In a recent survey, 80% of the pediatric cardiac centers in Europe reported using preventive drug therapy for LCOS in at-risk patients [21].

**Cardiovascular drugs**

In the pediatric cardiac setting, the use of cardiovascular drugs is often based on extrapolating the underlying pathophysiology and pharmacodynamics from adult studies, and on anecdotal experience. In 2008, Pasquali et al. published a survey on the use of off-label cardiovascular medications in children, as assessed by the Pediatric Health Information System. The study included observations from 31,432 patients, median age 10.4 months, and stated that 78% of all patients received at least one cardiovascular drug off-label; surgical CHD patients received a median of three drugs off-label. The risk of a neonate receiving at least one drug off-label was 11% higher than that of an older patient. The most common cardiovascular drugs used off-label were furosemide, epinephrine, dopamine, lidocaine, and milrinone.

The drugs currently used for the acute hemodynamic management of CHD patients are categorized into one or more of these functional classes:

1. Inotropic agents – catecholamines, phosphodiesterase III inhibitors, and calcium sensitizers
2. Chronotropes – isoproterenol
3. Vasoconstrictors – norepinephrine, phenylephrine, and vasopressin
4. Systemic vasodilators – nitroglycerine, sodium nitroprusside, hydralazine, phentolamine, phenoxybenzamine
5. Pulmonary vasodilators – inhaled nitric oxide, sildenafl, and prostaglandins
6. Others

The main inotropic and vasoactive agents are shown in Tables 17.1 and 17.2, together with the commonly used dosing regimens and specific responses.
Table 17.1  Cardioactive and vasoactive drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Doses</th>
<th>Receptors</th>
<th>Inotropy</th>
<th>Chronotropy</th>
<th>SVR</th>
<th>PVR</th>
<th>Renal vascular resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine</td>
<td>0.02–0.20 μg/kg/min</td>
<td>β₁, β₂ &gt; α₁</td>
<td>↑</td>
<td>↑</td>
<td>↔</td>
<td>↓</td>
<td>↓</td>
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<tr>
<td></td>
<td>Lower dose</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Higher dose</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dopamine</td>
<td>2–5 μg/kg/min</td>
<td>D₁, D₂</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
<td>↓</td>
</tr>
<tr>
<td></td>
<td>5–10 μg/kg/min</td>
<td>β₁, β₂ &gt; α₁</td>
<td>↑</td>
<td>↑</td>
<td>↔</td>
<td>↔</td>
<td>↓</td>
</tr>
<tr>
<td></td>
<td>&gt;10 μg/kg/min</td>
<td>α₁ &gt; β₁, β₂</td>
<td>↑</td>
<td>↑</td>
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<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>2–20 μg/kg/min</td>
<td>β₁ &gt; β₂, α₁</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>↔</td>
</tr>
<tr>
<td>Milrinone</td>
<td>Loading 25–75 μg/kg</td>
<td>PDE3 inhibitor</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
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</tr>
<tr>
<td></td>
<td>Infusion 0.25–0.75 μg/kg/min</td>
<td>↑ cAMP</td>
<td></td>
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</tr>
<tr>
<td>Levosimendan</td>
<td>Loading 6–24 μg/kg</td>
<td>Troponin C</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
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</tr>
<tr>
<td></td>
<td>Infusion 0.05–0.2 μg/kg/min</td>
<td>ATP-dependent K channel</td>
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<tr>
<td>Isoproterenol</td>
<td>0.01–0.2 μg/kg/min</td>
<td>β₁, β₂</td>
<td>↑</td>
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</tbody>
</table>

cAMP, cyclic adenosine monophosphate; ATP, adenosine triphosphate; D, dopaminergic receptor; PDE3, phosphodiesterase type 3; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance.

Table 17.2  Vasoactive drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Doses</th>
<th>Receptors</th>
<th>Inotropy</th>
<th>Chronotropy</th>
<th>SVR</th>
<th>PVR</th>
<th>Renal vascular resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine</td>
<td>0.02–0.20 μg/kg/min</td>
<td>α₁ &gt; β₁, β₂</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>0.02–0.3 μg/kg/min</td>
<td>α₁ (agonist)</td>
<td>↔</td>
<td>↔</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>0.02–0.05 units/kg/hour</td>
<td>V₁, V₂</td>
<td>↔</td>
<td>↔</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Nitroglycerine</td>
<td>0.2–10 μg/kg/min</td>
<td>Guanylate cyclase in the</td>
<td>↔</td>
<td>↔</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>0.2–5 μg/kg/min</td>
<td>vascular myocyte, tGMP</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Phenoybenzamine</td>
<td>0.25 μg/kg/24 hours</td>
<td>α₁ and α₂ (antagonist)</td>
<td>↔</td>
<td>↔</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Phentolamine</td>
<td>0.2–2 μg/kg/min</td>
<td>α₁ (antagonist)</td>
<td>↔</td>
<td>↔</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>1–5 μg/kg/min</td>
<td>Vascular myocyte</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Inhaled nitric oxide</td>
<td>10–40 ppm</td>
<td>Vascular myocyte, tGMP</td>
<td>↔</td>
<td>↔</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Sildenafil (PO, IV)</td>
<td>1–5 mg/kg</td>
<td>PDE5, tGMP</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Iloprost (nebulized inhalation)</td>
<td>2.5–5 μg, six to nine times/day</td>
<td>Vascular myocyte, tCAMP</td>
<td>↔</td>
<td>↔</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>

cAMP, cyclic adenosine monophosphate; CGMP, cyclic guanosine monophosphate; PDE5, phosphodiesterase type 5; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance; V, vasopressin; PO, oral administration; IV, intravenous.

Inotropic agents

The most commonly used inotropic agents are catecholamines and phosphodiesterase type 3 inhibitors. These agents exert their positive inotropic and chronotropic effects by increasing the intracellular calcium concentration via an increase in cyclic adenosine monophosphate (cAMP) and activation of the protein kinase pathway in cardiac myocytes (Figure 17.3). Cyclic AMP, in turn, activates calcium channels and leads to increased cytosolic calcium, which improves the contractility of the actin–myosin system through its binding with troponin C. Although these agents induce a rapid improvement in hemodynamics, their use may be limited by increases in the intracellular calcium concentration. Indeed, they may cause calcium overload and subsequent disturbances in cardiac rhythm and significant increases in myocardial VO₂.

β-Adrenergic agonists

Catecholamines play an important role in treating LCOS after cardiac surgery. Endogenous catecholamines such as dopamine, epinephrine, and norepinephrine are hormones and neurotransmitters that influence a multitude of physiological functions; however, synthetic catecholamines, such as dobutamine and isoproterenol, target specific receptors resulting in selective effects (Table 17.3). All endogenous catecholamines are synthesized from tyrosine, which undergoes several transformations to yield dopamine. A portion of the dopamine is then transported into vesicles from the cytoplasm where it is converted to norepinephrine, the main neurotransmitter in the human nervous system. The final step in the pathway, which converts norepinephrine to epinephrine, occurs in the adrenal medulla.

Human myocardium contains a relatively high proportion of β₂-adrenergic receptors. Both β₁ and β₂
Figure 17.3 Schematic representation of the postulated mechanism of action of β agonists, milrinone and levosimendan, in the myocardial cell. The mechanism of the positive lusitropic effect of levosimendan is not completely understood. PDE3, phosphodiesterase type 3; cAMP, cyclic adenosine monophosphate. (Source: Gillies et al. [159].)

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Receptor location site</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>α1</td>
<td>Vascular smooth muscle</td>
<td>Arterial vasoconstriction</td>
</tr>
<tr>
<td></td>
<td>Heart</td>
<td>↑ inotropic activity</td>
</tr>
<tr>
<td>α2</td>
<td>Vascular smooth muscle</td>
<td>Vasosconstriction of venous capacitance vessels</td>
</tr>
<tr>
<td></td>
<td>Presynaptic sympathetic nerve terminals</td>
<td>Local feedback, inhibition of norepinephrine release</td>
</tr>
<tr>
<td>β1</td>
<td>Heart</td>
<td>↑ inotropic and chronotropic activity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ AV node conduction velocity</td>
</tr>
<tr>
<td>β2</td>
<td>Vascular smooth muscle</td>
<td>Vasodilatation peripheral vasculature</td>
</tr>
<tr>
<td>D1</td>
<td>Bronchial smooth muscle</td>
<td>Bronchodilation</td>
</tr>
<tr>
<td>D2</td>
<td>Vascular smooth muscle (renal, splanchnic, cerebral)</td>
<td>Vasodilatation</td>
</tr>
<tr>
<td></td>
<td>Renal tubules</td>
<td>↓ Na reabsorption</td>
</tr>
<tr>
<td></td>
<td>Presynaptic sympathetic nerve terminals</td>
<td>↓ norepinephrine release</td>
</tr>
</tbody>
</table>

AV, atrioventricular; D, dopamine; Na, sodium.  
Source: Latifi et al. [27]. Reproduced with permission of Elsevier

Adrenoreceptors appear to be coupled to adenyl-cyclase stimulation, which induces the conversion of ATP to cAMP, the intracellular second messenger of β-adrenoreceptor stimulation. The half-life of catecholamines is approximately 2–5 minutes. As the breakdown of catecholamines by the catechol-O-methyl-transferase and monoamine-oxidase is ubiquitous, dosage adjustments are not necessary, even in patients with renal, hepatic, or any other organ dysfunction.

However, the use of catecholamines has several drawbacks. First, they further increase the VO₂, which is already increased after surgery and CPB [7–10]. The inotropic and chronotropic effects of catecholamines increase myocardial VO₂. This is particularly important in the neonatal myocardium, in which the functional reserve is limited and which operates under already maximal adrenergic stimulation. If such an increase is not accompanied by a proportional increase in coronary blood flow, a mismatch between myocardial VO₂ and DO₂ may result. Furthermore, catecholamines induce a dose-dependent increase in SVR and PVR, thereby increasing the afterload of both ventricles. Because of their strong inotropic effect, care should be taken when administering catecholamines to patients with dynamic LV outflow obstruction.

On the other hand, catecholamines also increase the overall metabolic rate, which manifests as an increase in the overall VO₂. The effects of catecholamines on cellular metabolism and thermogenesis are mediated via β₁, β₂ and, particularly, β₃-adrenergic receptor stimulation, and dopaminergic receptor stimulation, and might possibly be potentiated by α-adrenergic receptor agonists. All of these receptors are densely expressed at high levels in brown adipose tissue, which is abundant in human neonates, where they play a crucial role in non-shivering thermogenesis. Catecholamines, especially norepinephrine and dopamine, simulate heat production by stimulating fatty acid oxidation and uncoupling the respiratory chain from adenosine triphosphate (ATP) synthesis; thus, neonates may be particularly susceptible to the metabolic effects of catecholamines, which may increase VO₂ to much
higher levels than in older patients. Catecholamines also accelerate aerobic glycolysis and induce insulin resistance, a phenomenon that is exacerbated in younger patients [22], resulting in a concentration-dependent increase in blood glucose and lactate production (Figure 17.4) [23].

Long-term exposure of myocardial $\beta$-adrenoreceptors to circulating endogenous or exogenous catecholamines leads to receptor desensitization, which is mediated by uncoupling of the receptor–effector system and by a decrease in receptor density. $\beta_1$-receptor density is selectively reduced in patients with severe cardiac failure due to exposure to norepinephrine, which has a preferential affinity for $\beta_1$ receptors. Elevated norepinephrine levels in pediatric CHD patients correlate significantly with the size of the left-to-right shunt and the degree of PHT [24]; indeed, the number of right atrial $\beta$-adrenoreceptors in children with severe CHD is reduced to 50% [25]. The lowest receptor densities are found in critically ill neonates with congenital aortic stenosis or D-transposition of the great arteries [25].

**Epinephrine**

At low doses of epinephrine (<0.05 $\mu$g/kg/min), the $\beta_2$-adrenergic effects may predominate, leading to decreased SVR. At somewhat higher concentrations, $\beta_1$ receptors are activated, resulting in increased myocardial electrical conduction, increased sinoatrial node discharge, increased force of contraction, and increased rate of rise of ventricular intramural pressure. High concentrations of epinephrine may produce serious atrial and ventricular dysrhythmias if the myocardium is sensitized by infarction, surgery, or myocarditis. At even higher concentrations, vascular $\alpha$ receptors are activated, which increases the SVR. Even though epinephrine constricts renal and cutaneous arterioles, renal function and skin perfusion may improve due to increased CO. Very high infusion rates (>1–2 $\mu$g/kg/min), conditions in which the $\alpha_1$-adrenergic responses predominate, may exacerbate multi-organ system failure. During cardiopulmonary resuscitation, the $\alpha$-adrenergic-mediated vasoconstriction induced by epinephrine increases aortic diastolic pressure and, thus, coronary perfusion pressure, which is a critical determinant of successful resuscitation from cardiac arrest. The American Heart Association-recommended dose of epinephrine for children experiencing bradycardia, asystole or pulseless arrest is 0.01mg/kg intravenously (IV), which may be repeated at 3–5 min intervals, with a maximum 1 mg per dose in adult size patients [26].

Epinephrine is largely used in the postoperative management of CHD [21], although evidence-based data are currently lacking, and dosing regimens are extrapolated from adult studies. However, the amplitude of the hemodynamic response to epinephrine is difficult to predict. Although the effects of epinephrine are primarily dependent on the plasma concentration, a recent report shows that both age and body weight may play a role in the large between-subject pharmacokinetic and pharmacodynamic variability observed in children undergoing CHD.
surgery [23]. The younger and smaller the patient, the smaller the increase in heart rate and blood pressure for a given epinephrine concentration and severity of illness (Figure 17.5) [23]. It is likely that the postnatal development of the myocardial contractility is associated with changes in the modulatory effects of β-adrenoreceptor signaling.

**Dopamine**

Dopamine stimulates the dopaminergic D₁ (postsynaptic) and D₂ (presynaptic) receptors located in several vascular beds; it also binds α and β receptors, although with lower affinity. At low doses (<3 μg/kg/min), dopamine mainly binds dopaminergic receptors, thereby inducing vasodilation in the renal and splanchnic arterioles through complex second messenger systems. At moderate doses (>4 μg/kg/min) it stimulates β-adrenergic receptors and induces inotropic effects. Higher doses (>8 μg/kg/min) induce vasoconstriction via α-adrenergic receptor stimulation.

The sensitivity of infants to dopamine is controversial: neonates may exhibit a clinical response to doses as low as 0.5–1 μg/kg/min [27]. Li et al. [28] studied the effects of 5 μg/kg/min of dopamine in neonates undergoing the Norwood procedure. Dopamine did not increase DO₂ and seemed to cause an increase in myocardial VO₂.

A dopamine infusion of 5 μg/kg/min had a significant thermogenic effect, and termination of the infusion was associated with a substantial 20% reduction in VO₂ [28].

**Dobutamine**

Dobutamine is administered as a racemic mixture of two compounds, namely a strong β₁ agonist, and a strong α but weak β₂ agonist, and the end result is a drug with broad receptor specificity (Table 17.1). Despite its widespread use, the exact role of dobutamine in pediatric therapeutics remains unclear [27], and its use following cardiac surgery remains controversial because of excessive tachycardia and a variable effect on SVR. Dobutamine increases the myocardial VO₂ by up to 58% [29], and is frequently used to stress the myocardium (dobutamine stress test).

Comparison with newer inotropic drugs demonstrates similar improvement in stroke volume, although it induces a more profound decrease in LV filling pressures and vascular resistance than phosphodiesterase inhibitors [30]. Dobutamine induces a greater increase in heart rate than milrinone, and the beneficial increase in coronary blood flow may be outweighed by the increase in myocardial VO₂ [30]. Higher doses of dobutamine (>15 μg/kg/min) can predispose to the development of atrial or ventricular arrhythmias.
Inhibitors of phosphodiesterase type 3

The initial enthusiasm for the therapeutic use of bipyridines, which were developed in the 1980s to improve myocardial contractility in the chronically failing ventricle, had dampened by the early 1990s, after studies showing increased side-effects and mortality after long-term use. The development of oral formulations was halted, and currently only parenteral formulations are approved for short-term use in cases of acute or decompensated heart failure.

Bipyridines are highly selective for the cardiovascular tissues. The drugs selectively inhibit intracellular cardiac phosphodiesterase type 3, thereby slowing the degradation of cAMP. This results in a positive inotropic effect through increased intracellular calcium levels during excitation–contraction coupling, and a positive lusitropic effect through faster sequestration of calcium that is released into the sarcoplasmic reticulum due to the concomitant activation of phospholamban (Figure 17.3). Vasodilation occurs in both arterial and venous smooth muscle, via increased cAMP and activation of phospholamban. Arrhythmogenicity is mediated by an increase in intracellular cAMP and calcium levels. No tachyphylaxis is observed.

Amrinone

With amrinone, the prototype bipyridine, acts mainly on the vasculature; however, there is some debate around the relative contribution of the vasodilatory an inotropic effects [31–33]. Amrinone significantly reduces PVR in children with intracardiac left-to-right shunts [34]. Amrinone is metabolized in the liver via N-acetylation and is then excreted in the urine slow acetylators show a two-fold increase in the half-life, compared with that of rapid acetylators [35]. Clearance is reduced in patients with hepatic and renal failure, and reversible dose-dependent thrombocytopenia is common during prolonged therapy.

Milrinone

Milrinone is the most popular bipyridine drug, and is the one that has been subjected to careful evaluation in a placebo-controlled trial. The multicenter PRIMACORP trial demonstrated that the prophylactic administration of high-dose milrinone prevents the development of some of the clinical features of LCOS in infants and young children after heart surgery [16].

The drug shows consistent inotropic and vasodilatory effects. For example, Chang et al. reported that, when given to neonates with LCOS, milrinone (at a loading dose of 50 μg/kg, followed by an infusion of 0.5 μg/kg/min), increased the cardiac index from 2.1 to 3.1 mL/min/m², reduced filling pressures and reduced SVR by approximately 30% and PVR by about 25% [36]. These global improvements in hemodynamics were associated with an improvement in the myocardial VO₂/DO₂ ratio [36]. Compared with dobutamine, milrinone induced greater reductions in LV filling pressures and vascular resistance [30]. Unlike dopamine, milrinone does not increase myocardial VO₂ [30]. Instead, milrinone reduces coronary vascular resistance while having no significant effect on either coronary blood flow or myocardial VO₂ [30]. One experimental study showed that milrinone does not increase myocardial VO₂ or the myocardial OER, suggesting that it exerts a protective effect on the myocardium [17]. Furthermore, the positive lusitropic properties make milrinone a useful drug when LCOS results from diastolic ventricular dysfunction, which may be the case following tetralogy of Fallot repair.

The pulmonary vasodilator effect of milrinone has been demonstrated in infants with PHT, and is largely dependent on the degree of pre-existing PHT and the severity of ventricular dysfunction [36]. Milrinone induces pulmonary vasodilatation by increasing pulmonary vascular cAMP levels, and, possibly, by attenuating the release of inflammatory cytokines [37].

Milrinone has a half-life of about 1 hour, which is half that of amrinone; the half-life decreases linearly with age [38], and increases in the presence of renal failure. The PRIMACORP study demonstrated that high doses of milrinone (i.e. a bolus of 75 μg/kg, followed by an infusion of 0.75 μg/kg/min) led to a reduced risk of LCOS, whereas a low dose (a 25 μg/kg/min bolus followed by a 0.25 μg/kg/min infusion) had no effect. Hypotension is a commonly reported side-effect, occurring particularly during the administration of the loading dose, although ensuring an adequate preload can minimize it. It is likely that hypotension is responsible for the huge variability in the dosing regimens used at different centers, especially during the loading dose [21]. Many centers use milrinone without a loading dose, beginning the infusion before the end of CPB. Smith et al. examined a large cohort of more than 600 patients with CHD [39], and found that the risk of postoperative tachyarrhythmia increased up to three-fold when using with common dosing regimens of milrinone (a loading dose of 50 μg/kg, followed by a 0.25–1 μg/kg/min continuous infusion), independent of the concomitant use of catecholamines and of disease severity. Thrombocytopenia is less common (4% incidence) than observed with amrinone, and is seen when the infusion duration exceeds 3 days [40].

Levosimendan

Cardiotonic drugs that sensitize the myocardium to calcium represent a novel class of drugs designed to treat heart failure. Levosimendan, a pyridazine-dinitrilide first discovered by using cardiac troponin C as a target protein, has several desirable effects in the setting of cardiac surgery [41]. Levosimendan binds cardiac troponin C and stabilizes calcium-induced conformational changes, which in turn promotes the prolonged interaction between actin and myosin filaments during systole, and increases the force of myocardial contractions. Levosimendan has both vasodilatory and anti-ischemic effects, which are mediated by opening ATP-sensitive potassium channels in vascular smooth muscle cells. A recent study showed that it also acts on mitochondrial ATP-sensitive potassium channels.
to protect the heart against ischemia–reperfusion damage [42]. This finding may explain why short-term treatment with levosimendan may improve longer-term survival.

One of the advantages of levosimendan is related to its pharmacokinetic profile, which is unaffected by age or gender and makes it highly attractive for clinical use. Its biotransformation in the intestinal tract gives rise to an intermediate metabolite, OR 1855, which is inactive, and which is further metabolized in the liver by acetylation into OR 1896. OR 1896 is a long-lasting active metabolite whose concentration peaks at 36 hours after a 24-hour infusion and remains stable for up to 8 days; it is still detectable up to 12 days after levosimendan withdrawal [43]. Dosing adjustments are not required in patients with mild hepatic or renal failure.

The positive inotropic effect of levosimendan translates into a reduced ejection time, an increase in LV contractility, and reductions in the time taken to achieve peak systolic blood pressure and the time to systolic recovery, all of which are unmatched by either milrinone or dobutamine [44]. A phase I randomized blinded study of milrinone and levosimendan conducted in neonates [43] showed that patients in the milrinone group had a greater requirement for other inotropes during the first hours after surgery. Cerebral near-infrared spectroscopy (NIRS)-derived variables suggested that both drugs caused a time-dependent improvement in blood flow and oxygen availability, but infants receiving levosimendan showed significantly higher peripheral intravascular oxygenation and a lower difference in the central-to-peripheral temperature gradient [43]. In adult patients, Michaels et al. demonstrated a 20% increase in left ventricular ejection fraction and a 45% increase in coronary blood flow, despite a lower coronary perfusion pressure and a 9% reduction in myocardial oxygen extraction [29]. These observations were confirmed by Stocker et al. [17], who further demonstrated that levosimendan improved myocardial efficiency and did not increase the myocardial VO2.

The diastolic effects of calcium-sensitizing agents are more controversial because it was thought that they might impair the dissociation of myocardial actin–myosin cross-bridges, and theoretically reduce diastolic function. Because levosimendan dissociates from cardiac troponin C at a low calcium concentration, it does not impair diastolic function. In a study of piglets, Stocker et al. [17] demonstrated a reduced time constant for diastolic relaxation after early infusion of levosimendan, suggesting improved diastolic function. This may be of particular interest in patients with LCOS due to diastolic RV dysfunction, and in neonates in whom the heart has a higher water and protein content and is less compliant.

Levosimendan exerts vasodilatory effects by stimulating ATP-sensitive potassium channels in systemic, pulmonary, and coronary vascular smooth muscle cells [45]. Levosimendan has weak pulmonary vasodilator effects in the normal circulation [46], but has a potent effect in the pre-constricted pulmonary circulation [45]. In addition, it may attenuate endothelin-1-induced vasoconstriction, which would be of particular relevance in the post-CPB setting [47].

Two early phase III studies in adults reported that the use of levosimendan led to significantly reduced mortality in patients with heart failure following acute myocardial infarction (the RUSSLAN study) [48] and in those with chronic heart failure (the LIDO study) [49] when compared with placebo and dobutamine, respectively. Data from the REVIVE and SURVIVE studies [50] demonstrated significant short-term improvement in heart failure symptoms in adults. Two recent meta-analyses [51,52] showed that levosimendan led to a significant reduction in mortality compared with controls, with risk ratios between 0.4 and 0.5 in several settings in adult heart failure patients.

Because levosimendan does not increase the intracellular cAMP and calcium concentrations, it does not raise the heart rate and generate arrhythmias. Data from the REVIVE and SURVIVE studies, the two largest studies conducted to date, indicate that hypotension was most common side-effect of levosimendan, and was associated with a higher incidence of atrial fibrillation. Although less severe than that reported for milrinone, hypotension and tachycardia appear to be common at the beginning of the infusion, particularly during the loading dose [43, 53]. Levosimendan also shows excellent efficacy without a loading dose [43]. In contrast to those of catecholamines, the effects of levosimendan are not attenuated in patients with chronic heart failure, in whom β-adrenoreceptors are down-regulated, or by concomitant use of β-blockers. The development of tolerance has not been reported to date.

There are few published reports on the use of levosimendan after CPB in children, and there are currently no official indications regarding the use of levosimendan in patients less than 18 years old. However, the drug has been studied and used as a rescue therapy both in the pediatric intensive care unit and in the operating room. Reported pediatric experiences with levosimendan comprise observational studies [54,55] and four randomized and blinded trials [43,53,56,57]. In all, 645 patients have been examined in 14 studies. Levosimendan has been administered to children as an infusion of 0.05–0.2 μg/kg/min, with or without a bolus dose of 6–24 μg/kg. Recently, a group of experts published a consensus report regarding the use of levosimendan in cardiac surgery [58]. Also, a study entitled “Levosimendan in High Risk Patients Undergoing Cardiac Surgery” (HSR-LEVO) has been initiated and is currently recruiting. Levosimendan has the potential to become the drug of choice among agents with inotropic properties, possibly due to its cardioprotective qualities. As of this writing levosimendan is not approved by the U.S. Food and Drug Administration for use in any patients.

**Chronotropes**

**Isoproterenol**

Isoproterenol, a non-selective β agonist, is a synthetic derivative of norepinephrine. Isoproterenol has more chronotropic than inotropic effects, and lowers the SVR.
It is used to treat hemodynamically significant bradycardia; however, it is mainly used during cardiac anesthesia in the denervated heart immediately after transplantation, or in cases of complete atrioventricular block. High doses of isoproterenol can be arrhythmogenic and may induce ventricular tachycardia or fibrillation, and it is often used in electrophysiologic studies. Isoproterenol induces an increase in myocardial VO\(_2\), whereas DO\(_2\) decreases as a result of reduced coronary diastolic filling; this may exacerbate or induce ischemia. Therefore, patients receiving isoproterenol should be volume replete.

**Vasoconstrictors**

**Norepinephrine**

Norepinephrine has potent \(\alpha\)- and \(\beta_1\)-agonist activity but little \(\beta_2\) activity. Therefore, infusion of norepinephrine results in increased SVR because the \(\alpha\)-adrenergic stimulation is not opposed by \(\beta_2\) stimulation. Norepinephrine is used in the pediatric setting of shock with profound hypotension; however, it should be administered after intravascular volume repletion, and its use is best guided by knowledge of the CO and SVR. Norepinephrine increases afterload, but reduces myocardial VO\(_2\), due to a reflex reduction in heart rate. By increasing diastolic pressure, norepinephrine increases coronary perfusion.

However, injudicious use of norepinephrine compromises blood flow within organs, e.g., renal, splanchnic, and hepatic blood flow is reduced in healthy individuals. Infusion of norepinephrine may increase blood pressure and yet not improve clinical indices of perfusion, and this type of poor clinical response is usually associated with a persistent low cardiac index. Importantly, the pharmacokinetic of norepinephrine in children is not well known.

**Phenylephrine**

Phenylephrine is a pure peripheral \(\alpha_1\)-receptor agonist and is used as a bolus or infusion to treat acutely low systemic blood pressure or SVR. The pure \(\alpha_1\) effects can result in reflex slowing of the heart rate, although this is not as pronounced in young infants. Its main use in CHD is to acutely raise SVR in cases where either ventricle is compromised by outflow obstruction. Such is the case in tetralogy of Fallot, where low SVR leads to increased right-to-left intracardiac shunting and cyanosis [59], and in hypertrophic cardiomyopathy [60] or other left-sided obstructive lesions, in which the gradient across the obstruction is increased by low SVR. A bolus dosing of phenylephrine, such as used on CPB to increase perfusion pressure, is 0.5–5 \(\mu\)g/kg, whereas infusion doses range from 0.02 to 0.3 \(\mu\)g/kg/min.

**Arginine vasopressin**

Arginine vasopressin (AVP) plays a vital role in maintaining normal arterial blood pressure by regulating vascular tone, venous capacitance, and arterial resistance. The rationale behind the use of exogenous AVP in the critically ill patients is that neurohypophyseal stores of AVP may become exhausted, leading to vasodilatory shock [61]. Another theoretical advantage of AVP is that it does not rely on adrenergic receptors, which may be down-regulated in the presence of chronically elevated catecholamines. Also, signal transmission via adrenergic receptors may be impaired under conditions of metabolic acidosis. However, a recent meta-analysis showed that vasopressin and its analog, terlipressin, did not confer a survival advantage in adults suffering from vasodilatory shock [62]. Few reports have examined the use of AVP in children, and only two retrospective reports examined its use following CHD surgery [63,64]. A total of 17 neonates [63] and 11 infants and children [64] with low blood pressure and adequate cardiac function following cardiac surgery responded to the pressor action of AVP during the first hours after an AVP infusion ranging from 0.0001 to 0.002 units/kg/min. Plasma AVP levels were studied in three children, and demonstrated AVP depletion. On the other hand, safety data for AVP are lacking; a prospective randomized study of critically ill children requiring prolonged mechanical ventilation showed that AVP was associated with an increased incidence of oliguria and hyponatremia [65].

**Systemic vasodilators**

**Nitric oxide donors: nitroglycerine and sodium nitroprusside**

Nitric oxide donors are used to optimize ventricular loading conditions in patients with systolic dysfunction. Low-to-moderate doses of nitroglycerine (3 \(\mu\)g/kg/min) increase venous capacitance without affecting the arterial resistance vessels [66]. As a result, ventricular filling pressures fall, whereas the stroke volume is unaffected. High-dose nitroglycerine and nitroprusside increase venous capacitance and reduce SVR; thus, filling pressures fall and the stroke volume and CO rise significantly. Major indications for the use of nitroglycerine include myocardial ischemia, systemic hypertension, volume overload, congestive heart failure, and pulmonary edema. The net effect is usually an improvement in the myocardial oxygen-to-delivery ratio. Efficacy has been demonstrated following CHD surgery [67].

Tolerance occurs after more than 24 hours of IV therapy, and abrupt weaning after prolonged IV infusions may result in rebound hypertension. Extremely rare side-effects are methemoglobinemia and cyanide toxicity, which result from the release of nitrite ions when the drug is metabolized.

**Phenoxycbenzamine**

Phenoxycbenzamine is a long-acting \(\alpha_1\)- and \(\alpha_2\)-receptor blocker that covalently binds \(\alpha\)-adrenergic receptors and has a half-life of 24–48 hours. It is advocated by some groups for the routine perioperative management of infants undergoing cardiac surgery involving hypothermic CPB. Following the Norwood operation, systemic vasoconstriction occurs additionally in response to failing
systemic perfusion, as seen at \( \text{SaO}_2 > 80\% \), and is traditionally managed by manipulating the medical gases to increase PVR and lower SVR. Hoffman et al. carried out a prospective study of phenoxybenzamine use in patients who underwent the Norwood operation [68]. Patients received 0.25 mg/kg phenoxybenzamine at the start of CPB, followed by 0.25 mg/kg/24 hours for up to 48 hours postoperatively if the target \( \text{O}_2 \) delivery (\( \text{SvO}_2 > 50\% \)) and target Qp/Qs ratio (0.8–1.2) were not reached. There was no evidence of hemodynamic deterioration at high \( \text{SaO}_2 \) [68], suggesting that \( \alpha \)-adrenergic blockade is a more effective approach to modifying the intense sympathetically mediated vasomotor responses in these infants.

**Phentolamine**

Phentolamine is a reversible shorter-acting \( \alpha \)-receptor blocker with a half-life of 1–2 hours. Its use is justified by the observation of elevated plasma catecholamine concentrations and increased SVR following CPB. One study reported that administration of 0.2 mg/kg of phentolamine during cooling and rewarming periods during cardiac surgery reduced plasma lactate levels, indicating better tissue perfusion. In addition, the nasopharyngeal–rectal temperature gradient decreased four-fold, whereas systemic VO\(_2\) increased [69]. However, no one vasodilator appears to be superior to another.

**Hydralazine**

Hydralazine dilates pre-capillary arterioles. Most studies of hydralazine were performed in the 1980s, in which the drug was used to treat hypertension following CPB in adults. Hydralazine can be used to treat postoperative hypertension in children, or in other situations that require a reduction in preload, such as severe myocardial dysfunction and extracorporeal membrane oxygenation (ECMO). However, the vasodilatory effect is limited by reflex tachycardia; therefore, \( \beta \)-blockers and sodium nitroprusside are preferred.

**Pulmonary vasodilators**

In the early 1990s, PHT was a major cause of post-CHD surgery mortality [70]. Overall survival has improved since then and the reported incidence of severe PHT (defined as a ratio of pulmonary-to-systemic arterial pressure > 1) has dropped to 2% [71], most likely due to a better understanding of the pathophysiology of PHT, earlier surgical correction in patients at high risk of PHT, and refinement of intraoperative techniques, including ultrafiltration.

It is accepted that an important pathological characteristic of pulmonary vascular reactivity in patients with CHD is dysfunction of the pulmonary endothelium [72]. Such dysfunction suppresses the intrinsic endothelium-dependent vasodilatory mechanisms, including the nitric oxide cyclic guanosine monophosphate (cGMP) system. Cyclic GMP is generated by the interaction between nitric oxide (NO) and guanylate cyclase, and is the final messenger in the pathway that mediates vascular smooth muscle relaxation. It is metabolized by phosphodiesterase type 5, which is the major phosphodiesterase in the lung; phosphodiesterase type 5 expression is up-regulated in patients with PHT and after CPB, causing increased turnover of cGMP. A schematic representation of the mechanism of action of pulmonary vasodilators is shown in Figure 17.6.

There is always some degree of pulmonary endothelial dysfunction following CPB. Examples include systemic inflammatory responses and sequestration of activated neutrophils within the pulmonary microcirculation,

![Figure 17.6 Schematic representation of the postulated mechanism of action of pulmonary vasodilators in the pulmonary endothelial cell. iNO, inhaled nitric oxide; cGMP, cyclic guanosine monophosphate; cAMP, cyclic adenosine monophosphate; PDE3, phosphodiesterase type 3. (Source: Ghofrani et al. [160]. Reproduced with permission of Elsevier.)](image-url)
Inhaled nitric oxide

Inhaled nitric oxide (iNO) has been used for more than two decades to selectively reduce PVR. iNO produces pulmonary vasodilatation in ventilated lung regions by activating endothelial guanylate cyclase, resulting in increased levels of cGMP, which, in turn, relaxes pulmonary vascular smooth muscle. iNO crosses the alveolar–capillary membrane leading to immediate pulmonary vasodilation. High-affinity binding and immediate inactivation of iNO activity by hemoglobin limits the action of the drug in the pulmonary circulation.

An early study by Miller et al. reported that iNO concentrations as low as 2 ppm reduced PVR by approximately 40%, and improved CO by approximately 15% [75]. The pulmonary-to-systemic artery pressure ratio predicts the response to iNO, with a greater response seen in those with a high ratio (≥0.50). The use of iNO has become more common, and a randomized double-blind study demonstrated its usefulness as a prophylactic treatment in patients at risk of PHT: patients treated with iNO suffered fewer PHT episodes and could be extubated more quickly [76]. Morris et al. [74] demonstrated that iNO was as effective as hyperventilation for reducing PVR; however, unlike hyperventilation, iNO did not increase SVR or reduce CO. iNO significantly improves oxygenation, lowers the transpulmonary pressure gradient by 40–50%, and reduces central venous pressure by 15–20% in hypoxic patients undergoing Fontan-type procedures [77] and bidirectional Glenn anastomosis [78].

There are inherent problems with iNO, which may limit its use. These include a suboptimal response in some patients, the development of rebound PHT upon withdrawal after even relatively short periods of use, and the mode of delivery, which generally, though not necessarily, requires endotracheal intubation. Moreover, the individual responses to iNO are variable. Abrupt withdrawal of iNO or rapid reductions in the dose may lead to rebound PHT [79], even in patients with no pre-existing PHT. Rebound is due to the down-regulation of endogenous NO synthase in the pulmonary vascular endothelium and a reduction in guanylate cyclase activity. Rebound PHT responds to reintroduction of iNO; however, an interesting pharmacological solution is the addition of sildenafil, a selective inhibitor of phosphodiesterase type 5, which prevents the breakdown of cGMP until cGMP levels become naturally replete. As such, a single IV dose of 0.4 mg/kg sildenafil before weaning from iNO prevents rebound PHT in neonates and infants [80]. iNO also carries significant expense, with patient charges in the US often reaching several thousand dollars per day.

Inhaled nitric oxide has few side-effects. However, the binding of NO to hemoglobin gives rise to methemoglobin; therefore, methemoglobin levels should be routinely monitored, particularly in patients receiving prolonged therapy. Nitrogen dioxide is a by-product of NO administration and can injure the lung parenchyma; therefore, its concentrations should be maintained below 5 ppm. The initial dose of iNO is usually set at 20 ppm, and a reasonable attempt to wean the patient off it should be made every 12–24 hours. There is little evidence that doses higher than 20 ppm are more effective, and they should thus be avoided because of greater risk of nitrogen dioxide toxicity, methemoglobinemia, and rebound.

Inhaled nitric oxide has had an undisputed impact on the management of PHT, and continues to warrant consideration as adjunctive therapy for some of the more severe patients. However, a recent meta-analysis concluded that iNO does not reduce short-term mortality. It also concluded that there was insufficient information to determine whether it has an impact on neurodevelopmental outcome, long-term mortality, and length of hospital stay, while acknowledging the study limitations, which included concerns over methodological quality, sample sizes and patient heterogeneity [81]. iNO is not specifically approved by the US Food and Drug Administration (FDA) for the treatment of post-surgical PHT, although it is approved for the treatment of persistent PHT in term neonates.

Arginine and citrulline are substrates for NO synthase, and the levels of both are reduced after CHD surgery. Studies of both oral and IV preparations in addition to iNO have been conducted, but the results are inconclusive.

Sildenafil

Sildenafil is a selective inhibitor of phosphodiesterase type 5, which increases cGMP levels in the pulmonary vascular endothelium. When administered orally to
healthy subjects, the bioavailability of sildenafil is only approximately 40%. Also, critically ill children may show unpredictable enteral absorption, and therefore IV sildenafil may be more appropriate in such cases. Sildenafil is metabolized in the liver and has a half-life of about 4 hours. Oral pediatric doses are between 1 and 5 mg/kg, but the greater bioavailability of the IV preparations allows effective doses of 0.5 mg/kg.

Sildenafil is at least as effective as iNO for reducing increased PVR in children with CHD [82], and it enhances the pulmonary vasodilator effects of iNO [83]. The use of sildenafil facilitates the successful weaning of patients off iNO [80].

Nevertheless, unlike iNO, because sildenafil is relatively non-selective, systemic administration is associated with a significant increase in intrapulmonary shunting and a clinically non-significant fall in arterial blood pressure [82, 83], which may sometimes outweigh its benefits. Intrapulmonary shunting is caused by vasodilatation of the pulmonary arterioles supplying non-ventilated areas of the lung, and results in hypoxia.

Sildenafil has recently been the subject of substantial controversy in the US. Although currently approved for use in adults with PHT, sildenafil is used off-label to treat neonates, infants, and children with PHT. A recent randomized controlled trial of sildenafil for the long-term therapy of children with PHT, and subsequent long-term follow-up data, revealed an increased risk of death after treatment with high-dose sildenafil [84]; therefore, the US FDA released a strong warning against its use in children with PHT. The European Medicines Agency approved low-dose sildenafil therapy in such cases, as there is evidence that low doses are effective at 1 year, with no increase in the risk of death. These data warrant further scrutiny. Tadalafil and vardenafil are two other phosphodiesterase type 5 inhibitors that are currently under investigation.

**Prostaglandins**

Prostaglandins (PGs) are the main metabolites of the arachidonic acid pathway. They are generated and released by the endothelium, and bind to receptors on the underlying arterial smooth muscle, thereby activating adenylyl cyclase, increasing cAMP levels, and inducing smooth muscle relaxation. Although PGs are rapidly metabolized by the pulmonary circulation, doses large enough to induce pulmonary vasodilation also induce systemic vasodilation. Inhaled PGs show more selective vasodilator properties than IV preparations and, like iNO, they prevent a ventilation/perfusion mismatch by redistributing blood flow to the ventilated aerosol-accessible regions.

Prostaglandin E₁ (PGE₁) was the first PG to be isolated. It is used extensively to maintain the patency of the ductus arteriosus in neonates whose systemic or pulmonary circulation is dependent on ductal patency. In addition, IV PGE₁ has been used to treat PHT. Side-effects occur in 20–40% of patients treated with higher doses (0.05–0.1 μg/kg/min), but are reversible upon reverting to a low dose or discontinuing the drug. Nevertheless, the most common side-effects (i.e., hypotension, apnea and hyperpyrexia) may complicate the postoperative course and outweigh any potential benefits. Limited research has been conducted into the use of inhaled PGE₁.

Prostacyclin (PGI₂) was first identified in 1976, and early studies of the use of IV PGI₂ in children suggest that it induces highly selective pulmonary vasodilatation within the pulmonary vascular bed, where it is inactivated during a single circulation time. However, the efficacy and pulmonary selectivity of the IV PGI₂ formulation, epoprostenol, following CHD surgery is similar to that of IV PGE₁ [85]. The inhaled formulation, iloprost, also shows good pulmonary selectivity. It also has a longer half-life (25 min), although repeated inhalation is needed for optimum clinical effectiveness. Iloprost may be used as routine therapy of PHT in countries where iNO is not available because of its prohibitive cost [86], as it has been shown to have similar efficacy to iNO in children with CHD [87]. Finally, iloprost may be useful in children who do not respond to iNO therapy or as a rescue therapy when other treatments have failed [86]. Other PGI₂ analogs, such as treprostinil (inhaled) or beraprost (oral), may have potential utility for the treatment of postoperative PHT in children. See Chapter 28 for an extensive discussion of PHT.

**Other strategies to improve circulatory function**

**Corticosteroids**

The rationale for using corticosteroids is two-fold: they limit the inflammatory response after bypass and are an adjunct therapy that reduces the need for high doses of inotropes.

Corticosteroids exert their anti-inflammatory effects by modulating the transcription of RNA and the subsequent synthesis of proinflammatory proteins; the IL-6 to IL-10 ratio is the most commonly used marker for assessing the balance between proinflammatory and anti-inflammatory factors. Methylprednisolone is the drug of choice due to its anti-inflammatory potency and its reduced tendency to induce sodium and water retention. The dosing regimen used in children was extrapolated from adult regimens and was empirically set at 30 mg/kg prior to CPB, followed by 30 mg/kg at the start of CPB. However, a recent survey of 36 cardiac surgery centers showed that, despite the widespread use of corticosteroids (97%) during the perioperative period, administration and dosing regimens were mainly based on provider preferences [88]. Combined steroid treatment is associated with improved DO₂ indices, lower hyperthermia-related increases in VO₂, a reduced fluid requirement, and a shorter length of hospital stay [89]; combined treatment even improves myocardial protection [90, 91]. Altogether, modulation of CPB-mediated inflammation by corticosteroids seems clinically beneficial in pediatric patients, especially when targeted to younger and more complex patients.

The actions of corticosteroids on the cardiovascular system are mediated via both non-genomic and
genomic effects [92-94]. Corticosteroids increase the reuptake of norepinephrine by inhibiting the catechol-O-methyltransferase enzyme, leading to increases in the plasma norepinephrine concentrations. They also increase cytosolic calcium availability in myocardial and vascular smooth muscle cells, and improve capillary integrity in patients with capillary leak syndrome. Finally, they inhibit PGI₂ production and the induction of NO synthase, thereby limiting the pathologic vasodilation associated with the inflammatory response. Corticosteroids can be considered for children with LCOS; however, a formal definition of adequate steroid dosing is required because, at present, dosing seems to depend on institutional preferences/experiences. The use of even small doses, about 100 mg/m²/day of a hydrocortisone equivalent, may be sufficient for use as a “rescue protocol” in children with LCOS [95], thereby reducing the need for inotropes. This raises the question of a potential adrenal insufficiency in patients with postoperative LCOS, which is similar to what is seen in patients with septic shock, and can be reversed by the administration of a “substitutive” dosage range. This is still controversial, as a study by Suominen et al. [95] showed that plasma cortisol levels in patients were normal, even though they showed improved hemodynamics when given hydrocortisone.

Controversy regarding the perioperative use of corticosteroids is ongoing, and a very large study based on data obtained from the Pediatric Heath Information Systems Database, and including 46,730 children from 38 U.S. centers from 2003 to 2008, was unable to show that corticosteroids were of significant benefit during the perioperative period [96]. Also, the use of corticosteroids is associated with a greater risk of infection, a greater postoperative requirement for insulin, and, finally, longer length of hospital stay. The association with morbidity was more prominent in the low-risk group. Similar conclusions were drawn from a study restricted to neonates [97].

Thyroid hormone
Thyroid hormone levels are depressed after CPB [98]. Bettendorf et al. demonstrated that a daily infusion of triiodothyronine (T₃) (2 μg/kg body weight on day 1, then 1 μg/kg up to 12 days after surgery) led to a significant increase in the cardiac index [99]. A prospective randomized study [100] showed that T₃ supplementation (a bolus of 0.4 μg/kg immediately before CPB, 0.4 μg/kg on the release of the aortic cross-clamp, and then 0.2 μg/kg at intervals of 3, 6, and 9 hours after cross-clamp release) was beneficial for patients aged < 5 month and resulted in shorter time to extubation, improved cardiac function, and a reduced requirement of vasoactive support; these results were true regardless of surgical complexity. Mackie et al. [101] reported higher systolic blood pressures, and a shorter time until negative fluid balance was achieved in children undergoing reconstruction of the aortic arch treated with a continuous infusion of T₃ (0.05 μg/kg/hour for 72 hours postoperatively). T₃ appears to increase CO in patients with LCOS without any adverse events and without delaying postoperative recovery of thyroid function.

β-Adrenergic antagonists
Beta-blockers are beneficial for the management of chronic heart failure in both children and adults because they improve functional status. Patients with chronic heart failure show a down-regulation of β adrenoceptors due to increased sympathetic tone; β-blockers such as propranolol, metoprolol, and carvedilol increase the number of myocardial β adrenoceptors and improve myocardial function.

Beta-blockers can also be used for acute hemodynamic management in patients with CHD. The drugs reduce the effects of increased sympathetic tone on the RV infundibulum and heart rate in patients with tetralogy of Fallot, thereby improving RV filling. Esmolol, a short-acting β₁-selective antagonist, is well suited for the perioperatively treatment of tetralogy of Fallot patients [102]. Esmolol (100–700 μg/kg/min) controls postoperative hypertension following coarctation repair [103] and avoids reflex tachycardia that results from the use of selective vasodilators.

Calcium
Administration of calcium in the form of calcium chloride or calcium gluconate helps improve the inotropic function of the heart in patients with hypocalcemia. This is especially important in neonates, in whom plasma membrane Na⁺–Ca²⁺ exchange and Ca²⁺ influx channels play a greater role than the sarcoplasmic reticulum in regulating intracellular Ca²⁺ concentrations; therefore, neonates are highly dependent on extracellular calcium. Neonates receive significant amounts of citrated blood products; however, citrate binds Ca²⁺ and causes hypocalcemia. Calcium is also a major determinant of vascular smooth muscle tone because it plays an important role in excitation–contraction coupling in smooth muscle, and also functions as a vasoconstrictor.

However, routine administration of calcium salts upon termination of CPB is a subject of debate. First, if calcium levels return to normal as most patients are weaned off CPB, then calcium administration may not be required. Secondly, increasing evidence suggests that elevated intracellular calcium levels are associated with cell death and injury during ischemia and reperfusion injury [104].

Sodium bicarbonate
Buffering acidosis is essential in patients with, or at risk of, elevated PVR. The deleterious effect of acidosis on PVR, particularly in hypoxemic conditions, has been demonstrated experimentally more than 50 years ago [105], and the patterns of PVR variations as a response to changes in pH are shown in Figure 17.7. More recently, it has been shown that the administration of sodium bicarbonate to increase pH in infants with increased PVR reduces PVR by approximately 50% and increases cardiac index by approximately 35%, even if hypercapnia is present.
study performed to date showed that nesiritide does not affect mortality or prevent re-hospitalizations [110]. Also, there is no observable hemodynamic effect when it is used after CHD surgery [111].

**Fenoldopam**
Fenoldopam is a selective $D_1$-receptor agonist that possesses potent vasodilatory effects, particularly in the renal, mesenteric, coronary, and skeletal muscle vascular beds. Fenoldopam maintains adequate renal perfusion while concurrently reducing blood pressure. Few data are available regarding its use following CHD surgery. Small, albeit randomized, studies show that it is safe in neonates when used at a low dose (0.1 μg/kg/min) [112], and that a higher dose (1 μg/kg/min) has a beneficial effect on kidney function following CPB [113,114].

**Dopexamine**
Dopexamine is a synthetic adrenergic drug that activates both $\beta_2$ and $D_1$ receptors. Dopexamine has no effect on $\alpha$ adrenoreceptors. The main clinical effects are increased cardiac index and peripheral vasodilation, especially in the splanchnic vascular bed, increased diuresis and natriuresis. When compared with dobutamine, dopexamine resulted in a similar increase in cardiac index in children [115]. However, during treatment with dobutamine, children presented with significantly higher mean arterial pressures, whereas children treated with dopexamine had excessive increases in heart rate [115].

**Current practices**
A survey of 125 hospitals in 36 European countries conducted between January and August 2009 reported that 24 different drug regimens were being used for the prevention and treatment of LCOS in children [21]. In all, 40% of the respondents in the European survey [21], and 66% of attending physicians and physician fellows in a large pediatric teaching hospital in the US [116] stated that medical treatment of LCOS is constrained by a lack of appropriate drug regimens. Currently, there are no specific guidelines, and no dosing guidance is available for more than half of the available cardiac drugs. Dobutamine alone is licensed for use as inotropic support in children with LCOS in Spain and Germany [117,118], although, efficacy data are lacking in neonates.

Most European hospitals report using preventive drug therapy for LCOS, and approximately 80% selectively target the drug to at-risk patients. More than 70% of the preventive drug regimens include milrinone, but the dosage and duration of administration differ substantially among hospitals: the bolus dose varies from 20 to 300 μg/kg, the maintenance infusion ranges from 0.2 to 1 μg/kg/min, and the duration varies from 6 to 168 hours. The usual dose of milrinone appears to be less than that recommended by PRIMACORP [16], which may be due to concerns about the potential side-effects, particularly hypotension and age-specific pharmacokinetic
differences in drug elimination [38]. Dopamine, dobutamine, epinephrine, and levoisimendan were used less frequently in preventive drug regimens (each was used in about 16% of cases) and the dosages varied from 2 to 15 μg/kg/min for dopamine and dobutamine, and from 0.003 to 0.3 μg/kg/min for epinephrine. Levoisimendan was more consistent and was administered as a bolus of 12 μg/kg followed by a maintenance infusion of 0.1–0.2 μg/kg/min.

In keeping with the European survey [21], the six drugs that constitute 90% of total drug use for all kind of LCOS in children are milrinone, dopamine, dobutamine, epinephrine, levoisimendan, and methylprednisolone. Milrinone monotherapy was the preferred drug regimen (34%) for the initial treatment of LCOS with elevated SVR. Epinephrine was the preferred first add-on drug if the initial treatment was insufficient (24%), and levoisimendan was typically added as the next step (22%). Milrinone monotherapy was the treatment of choice for the initial treatment of LCOS with elevated PVR (17%). The most commonly used first and second add-on drugs were iNO (20%) and PGI₂ derivatives (22%). However, practices are not always in keeping with recommendations, and one reason for these differences may be the lack of sufficient evidence from well-conducted clinical trials in children with LCOS, which limits the strength of recommendations. As an example, the Spanish recommendations in children with CHD surgery include dobutamine or dopamine for the initial treatment of LCOS with elevated SVR, and iNO for the initial treatment of LCOS with high PVR. The first recommended add-on is epinephrine, and milrinone or nitroprusside come last in the treatment of LCOS with high SVR.

**KEY POINTS: IMPROVING POSTOPERATIVE OXYGEN TRANSPORT BALANCE**

- Inotropes, chronotropes, vasoconstrictors, vasodilators, and other drugs are all important strategies despite few controlled trials in pediatric cardiac surgery.
- Milrinone and epinephrine are the preferred drugs for prevention and treatment of LCOS, respectively.
- Levoisimendan has desirable properties as a non-catecholamine, calcium-sensitizing agent.

**Cardiopulmonary interactions**

Mechanical ventilation plays a crucial role in the hemodynamic management of patients following CHD surgery. It is easy to underestimate the effects of ventilation on the cardiovascular system or to misinterpret cardiopulmonary interactions as primary cardiovascular events. Both spontaneous and mechanical ventilation induce changes in intrapleural and intrathoracic pressure and in lung volume, which can independently affect the key determinants of cardiovascular performance: atrial filling or preload, the impedance to ventricular emptying or afterload, heart rate, and myocardial contractility.

In 1948, Cournand et al. [119] showed that CO was reduced in patients receiving intermittent positive pressure ventilation (PPV) via a mask. This study, one of the first to investigate cardiopulmonary dynamics during mechanical ventilation, showed that CO was inversely correlated with RV filling pressures, which were, in turn, directly influenced by the ventilator settings.

A reduction of functional residual capacity (FRC) after anesthesia and thoracic surgery may cause atelectasis, hypoxia, and respiratory failure. CPB and reperfusion result in an intense general inflammatory reaction and diffuse endothelial damage with an increase in vascular permeability, both of which result in pulmonary injury. Alveolar and interstitial edema, which may or may not be clinically apparent, reduce dynamic lung compliance (the ratio of the tidal volume to peak inspiratory pressure) and increase the ventilation/perfusion mismatch [14]. Mechanical ventilation reverses the inevitable reduction in FRC caused by anesthesia and thoracic surgery, but high mean airway pressures may be necessary to provide equivalent gas exchange in less compliant lungs. This can result in a decrease in CO. Three decades ago, Jenkins et al. [120] demonstrated the cardiopulmonary effects of stopping mechanical ventilation after open-heart surgery in 17 children: FRC, pH, and PaO₂ were significantly reduced, whereas PaCO₂ and RV stroke index significantly increased. The mean FRC during spontaneous ventilation was below normal levels, despite continuous positive airway pressure, and there was a significant increase in PVR in patients with an FRC that fell below 22 mL/kg while on spontaneous ventilation.

**Effect of changes in intrathoracic pressure**

**Right side of the heart**

In the absence of a left-to-right shunt, the CO is equivalent to the systemic venous return. The systemic venous return depends on the pressure gradient between the extrathoracic veins and the RA pressure. Spontaneous inspiration induces a negative intrapleural pressure and increases the RA transmural pressure (RA pressure – intrathoracic pressure). As a result, the RA increases in size and the RA pressure falls. This favors the venous return and increases RA filling. Conversely, during positive pressure inspiration, the RA transmural pressure decreases, the size of the RA decreases, and the RA pressure increases, thereby lowering the gradient for venous return and causing it to decelerate. Circulatory reflexes (adrenergic-mediated reductions in venous capacitance and renin–angiotensin–aldosterone system-induced volume expansion) increase the circulatory filling pressure in an attempt to maintain the pressure gradient for venous return.
There are certain clinical situations in which positive intrathoracic pressure may compromise CO secondary to impeding venous return. These include hypovolemia, gas trapping associated with obstructive airway disease, obstructive right heart lesions, and total cavopulmonary connection. In such situations, volume loading is frequently used to compensate and augment venous return. Also, adrenergic agonists and ventilatory strategies are used to reduce the intrathoracic pressure.

Positive pressure ventilation further compromises CO in the presence of diastolic dysfunction. Isolated RV diastolic dysfunction is seen in nearly 50% of patients with a tetralogy of Fallot repair [20] and can result in LCOS. If the patient’s clinical status allows, a method of ventilation that permits patient-initiated breathing (e.g., pressure support or volume support with patient trigger) will result in a lower intrathoracic pressure than if all breaths are ventilator-derived. It is also suggested that negative pressure ventilation, which increases pulmonary blood flow by up to 67% in patients suffering from LCOS due to RV diastolic dysfunction, might be a useful hemodynamic tool in such cases [121].

Left side of the heart
The aortic transmural pressure (aortic pressure – intrathoracic pressure) increases during spontaneous inspiration, due to the fall in pleural pressure. As such, the afterload of the LV increases, which may cause pulmonary edema in patients with poor LV function when weaning from mechanical ventilation. Conversely, PPV with positive end-expiratory pressure (PEEP) can reduce or overcome negative inspiratory swings in intrathoracic pressure. Also, by lowering the afterload, it can potentially restore hemodynamics. LV failure and pulmonary edema are also associated with an increased intrathoracic blood volume. By limiting venous return and lowering LV afterload, a positive intrathoracic pressure, or even simply the use of PEEP, can improve CO.

Pulmonary vascular resistance
Pulmonary vascular resistance is the main determinant of RV afterload and is directly affected by changes in lung volume. PVR depends on the balance between the vascular tone of the alveolar vessels, and that of the extra-alveolar or parenchymal vessels. PVR can increase at either extremes of lung volume, as shown in Figure 17.8. When the lung is inflated above the FRC, the alveolar vessels become compressed due to alveolar distension. As the lung volume falls towards the residual volume, the terminal airways collapse, which in turn causes alveolar collapse; this ultimately results in hypoxic pulmonary vasoconstriction. When ventilating near “normal FRC,” the impact on PVR and RV afterload is minimal. High-frequency oscillatory ventilation allows lung volume to be maintained near FRC, and avoids the detrimental effects of large swings in lung volume on PVR. Chapters 19 and 31 present further discussion about ventilatory strategies and cardiopulmonary interactions.

Delayed sternal closure
The sternum is often left open after complex neonatal surgery, or surgery in older infants and children with significant bleeding or tenuous hemodynamic status after a lengthy CPB run. Leaving the sternum open causes a substantial increase in the total respiratory system compliance. Pericardial and sternal closures produce constrictive effects and may interfere with efficient mechanical ventilation after cardiac operations. This is important for infants in whom considerable capillary leak and edema may develop after CPB, and in whom cardiopulmonary interactions have a significant impact on immediate postoperative recovery. Delayed closure is also used electively in high-risk neonates, as a means of maintaining hemodynamic and respiratory stability during the initial postoperative period [122]. Delayed sternal closure is not associated with an increased risk of surgical site infections. Significant hemodynamic changes are seen at the time of sternal closure: atrial pressure and heart rate increase, and mechanical ventilation requirements increase as a result of reductions in total respiratory system compliance, tidal volume, and expired CO₂ (Figure 17.9) [123]. Significant increases in the fraction of inspired oxygen, peak inspiratory pressure, and ventilatory rate may be
required to maintain tidal volume and gas exchange. After a sustained negative fluid balance is achieved, the sternum can be successfully closed within several days; a large retrospective study performed at a large tertiary care center suggested a mean of 3–4 days [122]. Chapter 26 contains further discussion of the effects of sternal closure.

**KEY POINTS: CARDIOPULMONARY INTERACTIONS**

- PPV can compromise right heart function by decreasing venous return and worsening pre-existing diastolic dysfunction.
- PPV can actually improve left heart function in heart failure by decreasing ventricular transmural pressure gradient.
- PPV near normal FRC has the least effect on PVR.
- Sternal closure increases the effect of PPV and may increase heart rate, atrial pressure, and decrease cardiac output.

**Monitoring**

Estimating the adequacy of oxygen delivery in pediatric patients with CHD is challenging. Intracardiac shunting and small patient size make techniques such as SvO$_2$ monitoring or thermodilution CO monitoring difficult. CO measurements alone might be misleading during the postoperative period. Normal CO might be inadequate at times of increased oxygen demand, and a lower CO might be sufficient during times of lower oxygen demand. Several markers that are associated with adverse clinical outcomes have been identified, but the inability to readily and reliably assess global and regional tissue perfusion remains a challenge in this patient group. A recent survey among North American and European anesthesiologists showed that only 34% of respondents monitored CO in high-risk surgical patients, and that about 90% believe their current hemodynamic monitoring and management could be improved [124]. Finally, hemodynamic monitoring includes various measurements, ranging from arterial pressure and heart rate monitoring to microcirculation and mitochondrial function monitoring.

**Clinical hemodynamic variables**

Although clinical hemodynamic variables such as blood pressure, arterial saturation, heart rate, venous pressure, and fluid balance have been shown to be poor predictors of adverse outcomes [125–127], these variables are the mainstay of critical care management in pediatric patients. The limitations of arterial saturation for estimating DO$_2$ during the period after the Norwood procedure have been highlighted by using simulations of the single-ventricle circulation [5]. Barnea et al. [5] demonstrated a non-linear relationship between DO$_2$ and SaO$_2$ (Figure 17.10) [5]. As SaO$_2$ increases, oxygen delivery increases, reaches a peak, and then decreases rapidly. Peak DO$_2$ occurs at
Figure 17.10 Systemic arterial oxygen saturation (SaO₂) vs. systemic oxygen delivery (DO₂). The curves were generated by setting the cardiac output (CO) at 300 and 450 mL/min/kg and varying Qp/Qs from 0.2 to 10. The short line on each curve represents the point at which Qp/Qs = 1. Note that similar low and high DO₂ can be generated with several combinations of CO and SaO₂. As an example, at a SaO₂ of 70%, DO₂ can range between 21.9 and 45 mL O₂/min kg, depending on CO. Note that in the region of the curves where Qp/Qs > 1, small variations in SaO₂ result in large changes in DO₂. As an example, for the curve generated by setting CO at 450 mL/min/kg, increasing SaO₂ from 80% to 85% decreases DO₂ from 34.1 to 14.6 mL O₂/min/kg. (Source: Barnea et al. [5]. Reproduced with permission of Lippincott, Williams & Wilkins.)

Qp/Qs < 1. However, following the Norwood operation, Qp/Qs is commonly about 1.5. When Qp/Qs > 1, slight increases in SaO₂ are associated with large decreases in DO₂ (Figure 17.10). Additionally, DO₂ is a non-linear function of CO, as shown in equation (17.9), and the value of SaO₂ at which DO₂ peaks is dependent on CO.

Although fluid balance is a commonly monitored parameter, factors such as bleeding and hypovolemia, use of perioperative ultrafiltration, use of diuretics, and postoperative acute kidney failure can intervene in this setting. The most important challenge is likely to be the assessment of acute fluid redistribution, which is a consequence of the inflammatory response to CPB, variable degrees of capillary leak syndrome, and concomitant organ dysfunction. It follows that fluid balance is not always a reliable marker of CO. On the other hand, the most critically ill patients require more initial fluid resuscitation; thus it is unclear whether fluid balance is simply the result of the severity of illness or is an independent contributor to multi-organ dysfunction. Recent data show a dose–response relationship between increasing degrees of fluid overload and the length of mechanical ventilation and intensive care unit stay [128], which underlines the detrimental impact of positive fluid balance on organ function in critically ill children. A novel concept was recently proposed for critically ill adults in whom worsening fluid overload (>15%) itself is viewed as a marker of severe kidney injury, which requires renal replacement therapy to prevent the water accumulation becoming worse [129]. Accordingly, when controlling for other organ dysfunctions, fluid overload > 15% on any given day is independently associated with the day’s oxygenation index in critically ill children [128]. This suggests that there is a threshold value beyond which intervention might be beneficial for improving outcomes. Chapter 8 contains an extensive discussion of the inflammatory response and fluid shifts after CPB.

**Assessment of cardiac output**

The main technologies and devices used to monitor CO are listed in Table 17.4 [130].

**Systems for monitoring cardiac output**

Intermittent thermodilution through a pulmonary artery catheter has been the gold standard method for CO monitoring since the late 1960s. This method is extremely invasive, so the use of the pulmonary artery catheter decreased in the 1990s. However, the method is still useful for monitoring RV output, pulmonary arterial pressure, and SvO₂. Development of the less invasive monitoring of CO using the esophageal Doppler started in the 1990s. However, the waveform is highly dependent on correct positioning of the sensor and requires frequent adjustments in terms of depth, orientation and gain to optimize the signal.

Miniature invasive systems rely on arterial pressure waveform analysis, which is based on the proportionality between the LV systolic ejection volume and the area under the curve of the arterial pressure waveform. The main drawback of these systems is that they are highly dependent on vasomotor tone and vascular compliance. Also, the non-linear pressure–volume relationship within the arterial circulation requires repeated recalibration by a compliance independent system. Transpulmonary thermodilution (TPTD) was developed in the 1990s. Although less invasive, a dedicated central venous catheter is required for the injection of the indicator, and a central arterial line for detection. According to the Stewart-Hamilton principle, CO is inversely proportional to the area under the indicator time curve. TPTD is now integrated into the PICCO® (Pulsion Medical Systems AG, Munich, Germany) and VolumeView devices (Edwards Lifesciences, Irvine, CA), which combine TPTD with the analysis of the arterial pressure waveform. Plethysmography allows continuous monitoring of the CO, and TPTD is used to perform repeated calibration of the device. Frequent recalibration is required when the vasomotor tone changes, which is the case in the postoperative cardiac setting. Furthermore, these devices allow the clinician to estimate the cardiac preload.

To obtain a reliable measurement of CO using TPTD, the following conditions must be met: constant blood flow; minimal loss of the indicator; complete mixing of the indicator in the blood, and a single passage of the indicator. Several of these conditions are violated after CHD surgery. The blood flow is not constant in the presence of valvular regurgitations. Left-to right intracardiac or extracardiac shunting (collaterals) results in loss of the indicator. Finally, there is always a degree of recirculation of the
<table>
<thead>
<tr>
<th>Technology</th>
<th>System trade name</th>
<th>Invasiveness</th>
<th>Mechanism</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary artery catheter</td>
<td>Vigilance</td>
<td>+++</td>
<td>Thermodilution</td>
<td>Gold standard for continuous CO monitoring</td>
<td>No dynamic parameters of fluid responsiveness</td>
</tr>
<tr>
<td>Calibrated pulse contour analysis</td>
<td>PICCO plus,</td>
<td>++</td>
<td>Transpulmonary thermodilution with pulse contour</td>
<td>Continuous CO monitoring</td>
<td>Requires specific femoral artery catheter</td>
</tr>
<tr>
<td></td>
<td>VolumeView</td>
<td></td>
<td>analysis</td>
<td>ScvO₂ with specific device</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Good accuracy.</td>
<td></td>
</tr>
<tr>
<td>Uncalibrated pulse contour analysis</td>
<td>LIDCO plus,</td>
<td>+</td>
<td>Lithium dilution</td>
<td>Continuous CO monitoring</td>
<td>CO less accurate</td>
</tr>
<tr>
<td></td>
<td>FloTrac,</td>
<td></td>
<td>Pulse wave analysis</td>
<td>Mini-invasive self-calibration system</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PRAM</td>
<td></td>
<td></td>
<td>Can be used with any arterial line and arterial pressure sensor</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td>Not enough validation studies</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LIDCO Rapid,</td>
<td>+</td>
<td>Pulse wave analysis</td>
<td>Continuous CO monitoring</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pulsioflex</td>
<td></td>
<td></td>
<td>Mini-invasive self-calibration system</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nexfin</td>
<td>0</td>
<td>Pulse wave analysis</td>
<td>Completely non-invasive</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Self-calibration system</td>
<td></td>
</tr>
<tr>
<td>Ultrasound</td>
<td>CardioQ</td>
<td>0+</td>
<td>Doppler ultrasound</td>
<td>Less invasive than arterial-based systems, qualifies for billable monitoring in the USA</td>
<td>Requires manipulation for proper position, potential for user variability</td>
</tr>
<tr>
<td>Bioreactance</td>
<td>USCOM</td>
<td>0</td>
<td>Suprasternal ultrasound</td>
<td>Non-invasive CO measurement</td>
<td>Intermittent, operator-dependent</td>
</tr>
<tr>
<td>Endotracheal bioimpedance</td>
<td>NICOM</td>
<td>0</td>
<td>Bioreactance</td>
<td>Non-invasive continuous CO monitoring</td>
<td>Few validation studies, many limitations</td>
</tr>
<tr>
<td></td>
<td>ECOM</td>
<td>+</td>
<td>Bioimpedance</td>
<td>Mini-invasive continuous CO monitoring</td>
<td>Few validation studies</td>
</tr>
<tr>
<td>Thoracic bioimpedance</td>
<td>BioZ</td>
<td>0</td>
<td>Bioimpedance</td>
<td>Non-invasive CO measurement</td>
<td>Requires specific arterial kit and endotracheal tube</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Negative studies in the critical care setting</td>
</tr>
</tbody>
</table>

+++ maximum invasiveness; ++, moderate invasiveness; + minimal invasiveness; O, non-invasive. CO, cardiac output; ScvO₂, mixed venous oxygen saturation; SvO₂, central venous oxygen saturation.

Source: Ramsingh et al. [130].
indicator, which increases in the presence of a right-to-left intracardiac shunting. Continuous CO monitoring is still feasible, although it should be viewed as a method that measures a trend rather than an absolute value.

Totally non-invasive systems based on bioimpedance and bioreactance systems have been developed recently and are available for CO monitoring. Chapter 10 presents further discussion of hemodynamic monitoring modalities.

### Ultrasound-based methods

Errors due to the angle of insonation, the assumption of specific flow profiles across the vessels when calculating average flows, and the cross-sectional area of the vessel being imaged are all important when assessing various ultrasound-based techniques. CO can be quantified during echocardiography, by measuring the aortic or pulmonary valve velocity–time integral, and the valve annulus diameter. The technique requires a trained operator and can be performed using transthoracic and transesophageal echocardiography (TEE). Transesophageal Doppler probes have been designed specifically to assess descending aortic flow and to calculate CO. Either a built-in nomogram or a M-mode measurement is used to calculate the aortic diameter. Decreasing probe-sizes allow placement in pediatric patients of ≥ 3 kg. Two major biases, however, may prevent the correct estimation of CO using transesophageal Doppler [131]. The first is highly operator-dependent because the device requires manual positioning of the probe for optimum signal acquisition. The second is the assumption that there is a constant flow between the ascending and the descending aorta, which is not always the case in the setting of CHD. Chapter 12 presents detailed information on TEE methods.

### Systems for monitoring functional hemodynamic parameters

Instead of monitoring a given parameter, functional hemodynamic parameters are used to monitor the effects of a stressor on a single hemodynamic parameter. To assess preload dependence, the stress is established in the form of a fluid challenge and the parameter monitored is the stroke volume or one of its surrogates. The effects of mechanical ventilation on preload and stroke volume, or variability in the inferior vena cava (IVC), are used to detect fluid responsiveness; the effect of passive leg-raising on the stroke volume and the effect of an end-expiratory occlusion on arterial pulse pressure are used to predict responsiveness to volume expansion. Chapter 10 presents additional information about these methods.

### Near-infrared spectroscopy (NIRS)

The principles underlying NIRS are discussed in Chapter 11. NIRS technology allows one to derive the average oxy-hemoglobin saturation in a volume of tissue approximately 2.5–3 cm deep to the skin. The parameter displayed is a relative number calculated using an algorithm calibrated from *in vivo* and *in vitro* cerebral models, and is termed rSO$_2$. The primary goal of NIRS is cerebral monitoring, and a > 20% decrease from baseline is associated with hypoxic–ischemic neural injury [132].

The NIRS concept has been extended from its initial purpose of cerebral monitoring, evolving into a monitor of global or regional oxygen saturation outside the brain. Phelps et al. [133] conducted a retrospective review of 50 infants who had undergone the Norwood procedure, and reported, albeit with large confidence intervals, that a cerebral rSO$_2$ value below 55% in the first 48 hours after surgery was highly predictive of an adverse outcome. Crowley et al. [125] found an association between an rSO$_2$ < 40% and postoperative creatinine clearance and length of hospital stay. NIRS probes can be placed over other areas to provide information about regional blood flow and oxygenation, and have been extensively used to monitor oxygenation in muscle, liver, and kidney. Owens et al. showed that children with renal rSO$_2$ < 50% for more than 2 hours had a significantly higher risk of kidney injury than those with normal renal rSO$_2$. require more ventilator days and greater vasoactive support [134]. Renal rSO$_2$ dropped precipitously in patients with impaired hemodynamics, as shown in Figure 17.11 [134]. Recently, renal rSO$_2$ monitoring provided evidence of abolition of renovascular autoregulation [135].

Hoffman et al. [136] designed an original two-site method using cerebral and somatic probes, and the

![Figure 17.11](image-url)
difference between the two regional circulations is used to provide additional information about vascular tone. Oxygen extraction by the brain is relatively high, and flow-metabolism coupling is achieved by an autoregulatory mechanism, meaning that changes in cerebral blood flow related to changes in sympathetic tone are minimal. By contrast, the kidney is normally a high-flow, low-extraction organ, with a high tissue oxygen saturation, and renovascular resistance is under tight sympathetic control. Normally, renal rSO₂ is 15–20% higher than brain rSO₂. Under stress conditions, brain circulation is maintained at the expense of somatic-renal perfusion, so a reduction in this differential might indicate circulatory impairment. Hoffman et al. [136] showed that a reduction in the difference between somatic and cerebral rSO₂, with a cut-off estimated to be below 10%, could be used to assess shock and the risk of anaerobic metabolism.

Several factors may interfere with the NIRS measurements. Those that are specific to its use as a cerebral monitor include PaCO₂, cerebral autoregulation, and extracerebral contamination of the signal, while others include light contamination, interference between the two probes, dark skin, bilirubin levels, profound polycythemia, the arteriovenous ratio in the tissue, and drugs that modify vasomotor tone. Since near-infrared light penetration is limited to approximately twice the emitter–detector distance, somatic NIRS in larger patients with significant tissue edema or adipose tissue may not be measuring rSO₂ in the intended organ or tissue, e.g. the kidney. The somatic NIRS readings must be interpreted with caution in these settings. The neonate without significant tissue edema with NIRS probe on the flank (renal rSO₂) was the basis for the Hoffman et al. study [136] and is likely the best candidate for current NIRS technology.

The utility of NIRS monitoring is still controversial. It is likely that both the amplitude and the duration of rSO₂ reductions, integrated in the area under the curve, require attention; however, the threshold for hypoxia has not yet been established. rSO₂ values below 50% or 45% are associated with an increased risk of anaerobic metabolism and lactate production. Because of the intra and inter-regional variability associated with measuring regional saturations by NIRS, the method can only be reliably used to monitor trends.

Mixed venous saturation
Mixed venous saturation (SVo₂) shows how much of the delivered oxygen is left over after the consumption by the tissues, and is therefore more directly related to tissue oxygenation than CO measurement.

If we ignore dissolved oxygen, then equation (17.1) can be rewritten as follows:

\[
OER = \frac{(SaO_2 - SVo_2)}{SaO_2} \quad (17.17)
\]

Thus

\[
SVo_2 = (1 - OER) \times SaO_2 \quad (17.18)
\]

and since SaO₂ is often kept > 0.9, one can roughly estimate that

\[
SVo_2 = 1 - OER \quad (17.19)
\]

This simple relationship indicates that SVo₂ is directly related to OER [137]. The critical OER level defined by the onset of anaerobic metabolism is approximately 0.5–0.6. Therefore, it follows that the critical SVo₂ is approximately 40–50%. SVo₂ < 50% should be carefully considered and acted upon, and SVo₂ levels between 50% and 70%, and therefore low, must be interpreted in the context of the adequacy of tissue oxygenation [138].

The O₂ extraction and thus venous saturation levels vary across various organs (Box 17.3) and SVo₂ is a mix of venous saturation of all organs. As CO falls, blood flow is redistributed to maintain vital organ perfusion. Oxygen saturation falls first in the IVC, and is accompanied by a less severe drop in SVo₂. As CO falls further, the SVC and jugular saturations begin to decrease. Figure 17.12 illustrates the relationship between CO and SVo₂ according to the Fick equation. The figure suggests that when CO is high, minor variations in CO are related to minor variations in SVo₂, and that when CO is low, large variations in CO are related to large variations in SVo₂. Thus, SVo₂ measurements perform poorly when SVo₂ is clinically irrelevant (high CO), but perform well in clinically relevant situations where DO₂ may be inadequate.

Box 17.3: Oxygen extraction ratio and mixed venous oximetry

Oxygen extraction ratios based on mixed venous oximetry
- 25% – normal
- 30–40% – increased
- 40–50% – impeding shock
- 50–60% – shock, elevated lactate levels

Normal oxygen extraction ratios for central venous oximetry
- Right atrium – 25%
- Jugular vein – 35%
- Superior vena cava – 30%
- Inferior vena cava – 20%

Source: Bronicki et al. [138]. Reproduced with permission of Lippincott, Williams & Wilkins.

A true SVo₂ should reflect complete mixing of the returning systemic venous blood, making the pulmonary artery the most accurate sampling site. However, placing a catheter in the PA is often impractical, undesirable, or invalid because of intracardiac shunting in CHD. The use of both RA and SVC saturations (ScvO₂) to estimate SVo₂ is controversial. The difference between ScvO₂ and SVo₂ is primarily due to mixing of less saturated blood from the coronary sinus in the RA, but the heterogeneity of flow and metabolic demand within and between organs under critical conditions, as well as decreased cerebral oxygen uptake during sedation, also play a role. However, there is an excellent correlation between SVo₂ and the ScvO₂ drawn from a thoracic central line, especially when the tip...
The Fick equation relating mixed venous saturation ($SvO_2$) to cardiac output. Where the curve is relatively flat, small errors in $SvO_2$ measurement are associated with large errors in the calculation of Fick cardiac output and its clinical interpretation. However, in this region, cardiac output is generous and tissue oxygenation is not a major clinical issue. Where the curve is relatively steep, the reverse is true, and cardiac output measurement may not give clear guidance in assessing adequacy of tissue oxygenation. This is the region where tissue oxygenation is a major clinical issue. Therefore, $SvO_2$ is less subject to error than cardiac output in assessing adequacy of oxygen delivery. (Source: Walley [137]. Reproduced with permission of American Thoracic Society.)

*Figure 17.12* The Fick equation relating mixed venous saturation ($SvO_2$) to cardiac output.

of the line is placed in the RA, with ScvO$_2$ overestimating $SvO_2$ by 3–8% [139].

$SvO_2$ should be measured continuously in settings in which clinically important minute-to-minute changes that would otherwise go undetected are possible. A recent study demonstrated the power of continuous ScvO$_2$ measurements for predicting adverse events following CHD surgery [125]. Significant ScvO$_2$ desaturations occurred mostly within the first 12 hours of surgery, and were correlated with the duration of mechanical ventilation, length of hospital stay and inotrope use, and lower creatinine clearance. A period of only 18 minutes at an ScvO$_2$ level of 40%, or <50% for more than 35 minutes was highly predictive of multi-organ failure, reoperation or reopening of the chest, and a need for extracorporeal support [125]. High ScvO$_2$ values had a strong negative predictive value, suggesting that avoiding lower ScvO$_2$ is a valid goal to decrease the risk of major adverse events. Tweddle et al. demonstrated that following the Norwood operation, reductions in ScvO$_2$ reflected tissue hypoxia despite apparently normal hemodynamic parameters, and that continuous ScvO$_2$ monitoring correlates with improved survival [127]. Furthermore, ScvO$_2$ monitoring was included in a hemodynamic strategy to improve systemic DO$_2$ based on intense afterload reduction using phenoxybenzamine [68]. Only 32% of the ScvO$_2$ variance could be explained by SaO$_2$, thereby emphasizing the role of ScvO$_2$ monitoring in this situation.

Following CHD surgery, $SvO_2$ can be overestimated in the presence of residual left-to-right shunting. Also, because sympathetic tone increases vascular resistance in splanchnic-mesenteric beds as CO falls, the relative contribution of desaturated blood from those regions to the measured $SvO_2$ level is reduced and critical regional ischemia may occur in the absence of a critical reduction in whole-body $SvO_2$. Furthermore, $SvO_2$ levels as low as 55% may represent ideal hemodynamics for a patient with a single ventricle [140] due to complete mixing of the arterial and venous blood. Finally, there are significant differences between continuous fiberoptic measurements and intermittent measurements, which necessitates repeated calibration of the continuous measurement instrument [141]. Chapter 10 contains further information about $SvO_2$ monitoring.

Blood lactate

The majority of the ATP pool is produced via oxidative phosphorylation, which generates 36 molecules of ATP per molecule of glucose. The first stage of oxidative phosphorylation is the conversion of glucose to pyruvic acid, which occurs in the cytoplasm. The second stage is the oxidation of pyruvic acid into acetylcoenzyme A, which occurs in the mitochondria as part of the Krebs cycle. Lactate is generated by the reaction between pyruvic acid and reduced nicotinamide adenine dinucleotide (NAD), and requires either oxygen for re-conversion into pyruvic acid or energy for conversion to glucose [142]. The normal lactate:pyruvate ratio is approximately 10:1.

Oxidative phosphorylation can only occur when the mitochondrial $P_O_2$ is > 1 mmHg (normally in the order of 4–20 mmHg). Connett et al. [143] defined the thresholds of cellular hypoxia more than 30 years ago. The first threshold is crossed when cellular oxygen decreases but ATP production is maintained at a level sufficient to match ATP demand by metabolic adaptation: increase in glycolysis and changes in the phosphorylation state of the mitochondria. The second threshold is crossed when the steady state of ATP turnover can only be maintained by supplementary production of ATP via anaerobic glycolysis. This is a low efficiency pathway which results in only two molecules of ATP per molecule of glucose, and leads to rapid ATP depletion in high-energy-consuming organs, such as the brain, liver, and kidney. At this stage, ATP production becomes oxygen-limited, a state that defines dysoxia.

The brain can use glucose or ketone bodies for ATP production, whereas myocytes preferentially use free fatty acids. During hypoxia, the consumption of glucose increases to 90% of the total substrate consumed. It follows, therefore, that excess lactate accumulates under anaerobic conditions. The normal reference value for lactate in critically ill patients is traditionally considered to be <2 mmol/L. Lactic acidosis develops when the lactate concentration exceeds 5 mmol/L. An animal study showed a rapid increase in lactate production following exposure to hypoxia: when $P_O_2$ decreased from 100 to 40 mmHg, lactate levels increased from 2 to 6 mmol/L within 15 minutes, reaching 10 mmol/L within 30 minutes [144]. Likewise, restoration of normal oxygen delivery...
Figure 17.13 Example of an algorithm for postoperative management of patients based on serial lactate determinations (the rhythm of lactate monitoring was 4 hours). This protocol resulted in a three-fold reduction in mortality in high-risk patients at the Cardiac Intensive Care Unit of the Miami Children’s Hospital. CPS, cardiopulmonary support; i.e. extracorporeal membrane oxygenation or ventricular assist device. (Source: Rossi et al. [147]. Reproduced with permission of Springer.)

results in a rather prompt return to normal levels [145]; the half-life of lactate in the blood is less than 10 minutes.

For many years, blood lactate levels have been seen as a reflection of CO, and have been used to assess the relationship between VO\(_2\) and DO\(_2\) to help predict outcomes in high-risk patients [125,146,147]. Charpie et al. monitored neonates after complex CHD surgeries, and found that increased initial lactate levels or an increase in lactate of 0.75 mmol/L/hour were associated with a poor outcome [146]. Rossi et al. incorporated serial lactate measurements into a therapeutic algorithm during the postoperative period [147]. Based on the blood lactate level, attempts were made to increase the DO\(_2\) by transfusions, increasing inotropic support, reducing systemic afterload, changing the ventilator settings, or decreasing the VO\(_2\) through the use of sedatives, analgesics, or neuromuscular blockade. The algorithm is shown in Figure 17.13. Blood lactate levels that continued to increase or remained persistently high (>10 mmol/L) despite maximal medical therapy were taken to indicate a requirement for mechanical cardiopulmonary support. This protocol resulted in a three-fold reduction in mortality in high-risk patients. Unlike SvO\(_2\) monitoring levels, lactate levels have the same significance in single-ventricle patients as they do in patients with biventricular physiology. A persistent lactate concentration > 10 mmol/L always indicates severe physiologic derangement and increased risk for mortality, and can be used as an indicator to initiate cardiopulmonary support [147].

Blood lactate levels may increase due to a disparity between the rate of peripheral glycolysis and mitochondrial oxidative capacity. Epinephrine increases this disparity via several mechanisms: increased muscular and hepatic glycogenolysis via a \(\beta_2\)-adrenergic pathway and via the sarcolemmal \(Na^+\)/\(K^+\)-ATPase stimulation; inhibition of glycogen synthesis; limitation of the rate at which pyruvic acid enters the Krebs cycle. As it accumulates, pyruvic acid is converted into lactate to preserve intracellular supplies of NAD and ATP. Lactate also accumulates if hepatic and renal clearance is impaired. Lactate delivery via red blood cell transfusions or CPB priming may also result in mild hyperlactatemia [148]. Therefore, mild hyperlactatemia cannot be used as an index of CO or expected outcome [9].

KEY POINTS: MONITORING

- Invasive and non-invasive cardiac output monitors in CHD surgery have limited utility and to date have not been demonstrated to improve outcome.
- NIRS as a monitor of tissue oxygenation can predict low CO and poor outcome.
- Mixed venous saturation is a good monitor of VO\(_2\)/DO\(_2\) balance and can be useful in patients at high risk for oxygen transport imbalance.
- Serial blood lactate measurements are an important monitor of inadequate tissue oxygenation which correlate with outcome in infant CHD surgery.

Extracorporeal membrane oxygenation support

Extracorporeal membrane oxygenation support (ECMO) is used for circulatory support in pediatric cardiac surgical patients suffering from refractory LCOS, persistent hypoxemia, arrhythmias, cardiac arrest, or failure to wean off CPB, when all residual anatomical lesions and PHT have been excluded. The hemodynamic and technical issues related to ventricular assistance are discussed in Chapter 32.

The Extracorporeal Life Support Organization registry received reports that 39% of pediatric patients receiving cardiac ECMO between 1986 and 2002 survived to hospital discharge [149]. Survival has not changed significantly over time, and increased slightly to 41% in 2004. However, only 24.8% of patients with single-ventricle circulation and bidirectional Glenn or Fontan physiology who required
ECMO survived to discharge; this has not changed either over time, as survival in infants with hypoplastic left heart syndrome supported with ECMO reported to the same registry between 1996 and 2000 was 28%. Such reports suggest that the outcomes for patients with single-ventricle circulation are substantially worse than those with two-ventricle circulation. The reason for this may be differences between institutions in patient selection, indication for ECMO, timing of initiation, ECMO management, and availability of a rapid-response ECMO team.

The following discussion focuses on hemodynamic issues related to ventricular assistance in patients with single-ventricle circulation. A recent report showed that the overall survival rate after ECMO in patients with single-ventricle physiology who underwent a systemic-to-pulmonary anastomosis was 48% [150]. Indications for ECMO were the strongest predictor of survival to discharge, and better survival rates were seen in patients in whom ECMO was initiated to support hypoxemia, compared with those in whom ECMO was initiated to support circulatory collapse; the hazard ratio for survival was 10.8 [150]. During ECMO, there is an ongoing need to balance systemic and pulmonary perfusion to prevent myocardial and systemic ischemia, which is caused by excessive run-off into the low-resistance pulmonary bed through the shunt. In addition, the volume load placed on the single ventricle may impair the recovery of myocardial function. However, maintenance of partial shunt patency (e.g., vascular clip producing 50–75% shunt occlusion) is recommended to avoid pulmonary injury due to ischemia–reperfusion, which results in an increase in PVR and alveolar–arterial O2 gradients, a reduction in pulmonary compliance, and higher mortality.

Patients with failing bidirectional Glenn or Fontan physiologies present additional challenges in terms of cannulation and circulatory support with ECMO. They have significantly increased systemic venous pressures, which are likely to reduce cerebral and other end-organ perfusion pressures and compromise DO2 at baseline. The increase in intrathoracic pressure during cardiorespiratory resuscitation may restrict pulmonary blood flow in the Fontan or bidirectional Glenn circulation, thereby increasing cerebral venous pressure and further limiting cerebral perfusion. ECMO cannulation of bidirectional Glenn patients is particularly challenging due to the separation of the systemic venous drainage (the SVC drains to the pulmonary artery and the IVC drains to the RA). If the femoral cannula is placed first, this may delay decompression of the SVC, which, combined with a low systemic blood pressure, places patients at high risk of neurologic injury. Also, a single venous cannula is insufficient for venous drainage in the Fontan circulation; however, cannulation of multiple central veins may also be limited due to vessel occlusions resulting from previous vascular injury. Booth et al. undertook a retrospective review of patients with bidirectional Glenn or Fontan operations requiring ECMO from 1984 through 2002 [151], and showed that the success of ECMO support in patients with refractory LCOS is related to good myocardial function, or to a Fontan takedown.

**Postoperative management: lesion-specific**

**The Norwood procedure**

Following the Norwood procedure, the neonate has a unique convergence of physiologic vulnerabilities: myocardial dysfunction following ischemia, reperfusion and CPB, potential limitations of a morphologically right single ventricle, potential aorto-coronary flow limitation, and intrinsic inefficiency of the parallel circulation. The Sano modification (RV-to-PA conduit) has proven to increase the very short-term survival vs. conventional systemic arterial-to-PA shunt by improving the coronary perfusion of the single ventricle [152]; however, long-term results did not improve. By using computer simulations to study the single-ventricle circulation, Barnea et al. [5] has provided improved interpretation of the oxygenation parameters. He demonstrated that slight increases in SaO2 may be associated with large decreases in DO2 (Figure 17.10). Also, high values of Qp/Qs are always associated with low DO2, which is only partially compensated by increases in CO. Therefore, ideally, Qp/Qs should be kept below 1.5.

Traditionally, SaO2 has been used as a rough index of Qp/Qs balance, and systemic vasoconstriction reported in response to failing systemic perfusion at SaO2 > 80%. More recently, SvO2 > 50% and a Qp/Qs ratio between 0.8 and 1.2 have been provided as targets for hemodynamic optimization [68]. However, taken alone, SaO2, SvO2 or the Qp/Qs ratio cannot be used to maximize DO2, and equation (17.9) shows that DO2 is a complex function of both the CO and the Qp/Qs ratio. The index that should best guide therapy to increase DO2 is the oxygen excess factor (OEF):

\[
OEF = \frac{DO2}{VO2}
\]  

(17.20)

If dissolved oxygen is ignored, then this can be rewritten as

\[
OEF = \frac{SaO2}{(SaO2 – SvO2)}
\]  

(17.21)

A linear relationship has been demonstrated between OEF and DO2, irrespective of the CO [5]. The normal ratio is of four to five times the amount of DO2 to VO2. It is commonly accepted that OEF should be beyond 3.5 following the Norwood procedure, and any intervention that increases OEF is considered beneficial. Li et al. [153] demonstrated that the largest amount of DO2 variability is due to Qs and SVR, and vasodilation of the systemic circulation is acknowledged as a major contributor to the improvement of DO2. Manipulations of the pulmonary circulation have only minor effects [153]. Accordingly, Hoffman et al. [68] demonstrated that the most effective approach to improve the inefficiency of the single-ventricle circulation is to alter the intense sympathetically mediated...
systemic vasoconstriction using potent α-adrenergic blockers, such as phenoxybenzamine.

**Bidirectional Glenn anastomosis and Fontan operations**

Low cardiac output syndrome is the main cause of morbidity and mortality in this group. As shown in equation (17.15), following the bidirectional Glenn anastomosis, \( \text{DO}_1 \) is a complex function of \( \text{CO} \) and \( Q_{\text{SVC}}/Q_{\text{IVC}} \) ratio, where \( Q_{\text{SVC}} \) equals \( Q_p \). In the absence of an RV, \( Q_p \) is a passive diastolic flow, extremely sensitive to changes in the intrathoracic pressure. \( Q_p \) is enhanced during spontaneous inspiration (due to negative pleural pressure), and reduced when the intrathoracic pressure is made more positive. Therefore, the key to optimizing \( \text{CO} \) often lies in achieving early tracheal extubation, as advocated by Fontan himself. Negative pressure ventilation has been attempted in Fontan patients with a LCOS in whom early extubation was not possible: pulmonary blood flow increased by 42% and \( \text{CO} \) improved by an increase in stroke volume [154]. On the other hand, oxygenation is significantly improved by pulmonary vasodilators, which facilitate the passive flow into the pulmonary arteries and increase \( Q_p \). When given in hypoxic patients with a bidirectional Glenn anastomosis or after Fontan operations, iNO lowers the transpulmonary gradient by 40–50% and decreases the central venous pressure by 15–20% [77, 78]. In such situations, the addition of 0.5 \( \mu \text{g/kg/min} \) of milrinone to the regimen results in a synergistic effect, with a further fall in the transpulmonary gradient and a significant improvement in the oxygenation indices [155]. Other factors may alter oxygenation and are less susceptible to medical therapy: pulmonary venous admixture, systemic venous collaterals, and pulmonary arteriovenous malformations.

A unique consequence of the circulation following the Glenn anastomosis is that cerebral and pulmonary circulations are connected exclusively in series with each other. Thus, the cerebral and pulmonary autoregulatory mechanisms are in direct competition with each other: the brain vasculature dilates in response to hypercarbia and the lung vasculature vasoconstricts, and the opposite holds true for hypoxia [156]. The result is that the cerebral autoregulatory feedback loop overrides the pulmonary one, and hypercarbia markedly increases cerebral blood flow, and, as a consequence, \( Q_p \), oxygenation indices, and the global \( \text{CO} \). Oxygen has little impact. In the absence of systemic hypotension, manipulation of systemic blood pressure will not affect cerebral blood flow and oxygen balance because cerebral pressure autoregulation is intact.

**Tetralogy of Fallot repair**

After repair of tetralogy of Fallot, an LCOS is seen in nearly 50% of patients, as a result of RV diastolic failure [20]. This is most likely the result of the exposure of the hypertrophied RV to CPB and reperfusion injury. RV function may further alter due to right ventriculotomy, and especially when the incision is extended across the pulmonary annulus. Transannular patches result in massive pulmonary regurgitation and RV volume overload. In addition, if the pulmonary arteries are hypoplastic, the RV afterload is increased by this factor. Finally, there is invariably some degree of right bundle branch block after surgery, causing ventricular asynchrony.

Because systolic function is intact, inotropic agents are of little benefit. LCOS results from inadequate RV filling, which is compounded by a reduction in the effective compliance of the LV. During diastole, the hypertensive RV alters the normal trans-septal pressure gradient, causing the ventricular septum to bow into the LV, compromising ventricular filling [20]. Spontaneous ventilation, or negative pressure ventilation if the patient’s clinical status does not allow extubation, has been shown to improve hemodynamics [121,157]. Fluid administration is of limited benefit, because it increases the RV end-diastolic pressure and volume, and rapidly results in RV dilation, tricuspid regurgitation, and further decrease in RV output. Lusitropic agents such as milrinone, and controlling the heart rate and RV infundibular hypercontractility with low dose β-blocking agents such as esmolol may be effective in LCOS after tetralogy repair.

Chapters 21–28 each contain detailed discussions about hemodynamic considerations and management of specific cardiac lesions.

**Selected references**

A full reference list for this chapter is available at: http://www.wiley.com/go/andropoulos/congenitalheart


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Introduction

The practice of pediatric cardiovascular anesthesiology has evolved significantly over the years, expanding beyond the operative setting to many non-surgical environments. Anesthetic care for infants, children, and adolescents who have, or are at risk for, cardiac rhythm disturbances is now provided at various locations, including operating rooms, critical care units, emergency facilities, treatment rooms, and cardiac catheterization/electrophysiology laboratories. The same is true for other patients with congenital heart disease (CHD) beyond childhood. General knowledge of arrhythmia diagnosis and management is essential to anesthetic care in any of these settings, although in some cases, consultation with a specialist is required. This chapter provides a practical approach to pediatric cardiac arrhythmias and rhythm disturbances most commonly affecting patients with CHD, focusing on diagnosis, mechanisms, and acute management strategies. A brief review of anti-arrhythmic drug therapy and the basic principles of cardiac pacing in children, as applicable to the practice of anesthesia, is also presented.

Cardiac rhythm disturbances

Sinus bradycardia

Sinus bradycardia is characterized by a heart rate below the norm for the patient’s age and by a normal, sinus P wave. Slow heart rates can be observed during sleep or may be secondary to a high vagal tone. During significant sinus bradycardia, an escape rhythm may arise from the atrium, junction, or ventricle. In otherwise healthy children, this is usually a benign rhythm with no hemodynamic consequences. Patients with certain forms of CHD, however, are more prone to slow heart rhythms that may indeed be clinically significant. Those with heterotaxy syndromes are included in this category because of the absence, displacement, or hypoplasia of the true sinus node [1].

Intraoperatively, sinus bradycardia can result from vagal stimulation during induction of anesthesia, laryngoscopy, endotracheal intubation, or tracheal suctioning. Sinus bradycardia may also be related to drug administration (e.g., opioids) or other mechanisms of increased parasympathetic activity. This type of sinus bradycardia rarely results in significant hemodynamic compromise and can usually be treated by removing the stimulus or by administering a chronotropic agent such as atropine or epinephrine (Box 18.1). Slow sinus rates can be seen after interventions such as closure of atrial septal defects (ASDs) and cardiac transplantation.

Sinus bradycardia can also be due to hypoxemia, hypothermia, hypotension, drugs, acidosis, electrolyte abnormalities, or increased intracranial pressure. Hypoxemia-related bradycardia should be treated promptly with oxygenation and ventilation as appropriate. The approach to other forms of secondary sinus bradycardia should...
focus on addressing the underlying cause. For worrisome low heart rates, particularly in small infants, drugs such as atropine or glycopyrrolate should be considered. Ongoing bradycardia with clinical evidence of compromised cardiac output requires immediate escalation of therapy that, in most cases, includes epinephrine administration, cardiopulmonary resuscitation, and consideration of temporary pacing.

**Low atrial rhythm**
A low atrial rhythm is characterized by atrial activation that spreads upward from a focus on the low atrium. The electrocardiogram (ECG) shows inverted P waves in the inferior leads (II, III, and aVF). A slow atrial rhythm implies that another region of the heart has assumed the pacemaker activity of the sinus node. Although this rhythm may be associated with conditions that affect sinus node function, intraoperatively, it is most commonly the result of surgical manipulation (Figure 18.1). In most individuals this is a normal variant, and rarely has hemodynamic consequence.

**Sinus node dysfunction**
Sinus node dysfunction, often termed sick sinus syndrome, encompasses a spectrum of disorders characterized by slow or irregular heart rates that have a variety of escape rhythms and that frequently alternate with periods of tachycardia. The respondent tachycardia may be atrial tachycardia, atrial flutter, or atrial fibrillation. The term tachycardia-bradycardia syndrome is frequently used to characterize this association. The surgical interventions most likely to be associated with sinus node dysfunction include extensive atrial baffling procedures, such as Mustard and Senning operations, and the Fontan procedure. The management of symptomatic patients may include pacemaker implantation, pharmacological therapy for tachyarrhythmias, atrial anti-tachycardia pacing, and, in some cases, transcatheter or surgical ablation.

**Sinus tachycardia**
Sinus tachycardia is more commonly seen in the perioperative period than sinus bradycardia. It is often the result of painful stimuli or stress, hypovolemia, anemia, medications (e.g., inotropic agents), a high catecholamine state, surgical manipulation, or fever. Sinus tachycardia can often be differentiated from pathologic supraventricular arrhythmias by its variability in rate and its normal P-wave axis. Treatment is directed at the underlying cause. Prolonged periods of sinus tachycardia may impair diastolic filling time, limit ventricular preload, and compromise systemic cardiac output. Patients at higher risk of hemodynamic compromise are those with substantial ventricular hypertrophy or non-compliant (“stiff”) ventricles with associated diastolic dysfunction, such as in certain types of cardiomyopathies or obstructive outflow lesions (e.g., tetralogy of Fallot).
Junctional rhythm
Junctional rhythm is characterized by QRS complexes with a morphology identical to that of sinus rhythm without preceding P waves. This arrhythmia is thought to originate in the bundle of His. It often occurs in patients with sinus bradycardia or sinus node dysfunction. In this rhythm, there is normal atrioventricular (AV) nodal conduction, but it is sometimes difficult to determine this if the junctional beats are slightly faster than the atrial beats or there is 1:1 ventriculoatrial (V:A) conduction retrograde through the AV node. During surgery, this may occur as a result of cardiac manipulation and dissection around the right atrium. In addition to the ECG features described, the arterial and venous pressure waveforms can change during junctional rhythm (Figure 18.2). The central venous pressure tracing may show a tall a wave, termed a cannon a wave, which is due to late atrial contraction against a closed tricuspid valve (delayed retrograde depolarization of atrial tissue). An associated decrease in stroke volume and cardiac output, resulting from the absence of the normal atrial systolic contribution to ventricular filling, may manifest as a reduction in systemic arterial blood pressure. Temporary atrial pacing at 10–20 beats/minute (bpm) above the junctional rate can be used to document normal AV nodal conduction, and it frequently restores AV synchrony.

KEY POINTS: CARDIAC RHYTHM DISTURBANCES

- Sinus bradycardia may be due to vagal stimulation or drugs; it is important to exclude hypoxemia, hypothermia, hypotension, acidosis, electrolyte abnormalities, or increased intracranial pressure as potential etiologies.
- Low atrial rhythm is usually due to surgical manipulation.
- Sinus node dysfunction is more commonly seen after Mustard, Senning, and Fontan operations.
- Sinus tachycardia may be due to painful stimuli/stress, hypovolemia, anemia, medications, a high catecholamine state, surgical manipulation, or fever; treatment should be directed at the underlying cause.
- Junctional rhythm may occur due to surgical manipulation/dissection around the atrium; the central venous pressure tracing characteristically displays a tall a wave, and blood pressure may decrease due to loss of the atrial kick.

Conduction disorders
Bundle branch block
In the unoperated patient, bundle branch block is an uncommon ECG finding. An incomplete right bundle branch block (RBBB) pattern or intraventricular conduction delay can be seen in patients with right ventricular volume overload (e.g., ASDs, anomalous pulmonary venous drainage). In rare cases, a RBBB can be congenital and idiopathic. An RBBB pattern is frequently seen in postoperative patients after interventions for lesions such as tetralogy of Fallot, right ventricular outflow tract pathology, and AV septal defect (AVSD; also referred to as AV canal or endocardial cushion defect). This conduction abnormality may be related to a ventriculotomy incision, resection of infundibular muscle, damage to the moderator band, or, in some cases, closure of a ventricular septal defect (VSD). A left bundle branch block (LBBB) pattern is uncommon but may be found after surgical procedures involving the left ventricular outflow tract.

Atrioventricular block
First-degree AV block
First-degree AV block is characterized by a prolonged PR interval beyond what is considered normal for age. Each P wave is followed by a conducted QRS complex. This type of rhythm disturbance can be a normal variant in healthy individuals but can also be seen in a variety of disease states (e.g., structural heart defects associated with stretching of the atria, rheumatic fever). In general, a prolonged PR interval in an otherwise healthy child is a benign condition and requires no treatment.
Second-degree AV block

There are four types of second-degree AV block. The two predominant types, Mobitz type I (Wenckebach) and Mobitz type II, both involve a periodic failure to conduct atrial impulses to the ventricle. In type I second-degree AV block, the PR interval lengthens progressively until the next atrial impulse cannot be conducted to the ventricle. These failures of conduction manifest on the surface ECG as P waves without associated QRS complexes and concomitant shortening of the RR intervals (Figure 18.3). This rhythm disturbance can occur during periods of high vagal tone and is generally considered a benign phenomenon that requires no therapy.

In the less frequent type II second-degree AV block, there is a constant PR interval before an atrial impulse that suddenly fails to conduct. This conduction abnormality is more concerning because of its potential for progression. It can be seen in patients after surgery for CHD and is thought to be due to damage to the His bundle or distal conduction system.

The third type of second-degree AV block is two to one AV block (2:1). In 2:1, every second P wave is blocked. In most cases, this is a type of Mobitz type I or Wenckebach block and is secondary to high vagal tone. It is rare for 2:1 to progress to a higher degree of AV block or to require treatment.

The fourth type of second-degree AV block is high-grade AV block, which is evidenced by two or more non-conducted P waves in succession that would normally be expected to conduct. Temporary pacing and close patient observation may be warranted because hemodynamically significant bradycardia or continued progression of the conduction deficit may ensue.

Third-degree (complete) AV block

Third-degree AV block is characterized by the total failure of atrial impulses to be conducted to the ventricles. There is complete dissociation of the electrical activity between the atria and ventricles, and the ventricular rate is usually slow and regular. In third-degree AV block, the ventricular escape rate may be narrow (if originating from the perinodal region) or wide (if originating from within the ventricle). The diagnostic feature on the ECG is that all atrial impulses that should be conducted to the ventricle fail to do so (Figure 18.4).

Complete AV block may be either congenital or acquired. Congenital complete AV block in infants with otherwise structurally normal hearts may be due to intrauterine exposure to maternal antibodies associated with collagen vascular diseases. Patients at high risk of complete AV block include those with congenitally corrected transposition (L-transposition of the great arteries with ventricular inversion) and those with polysplenia (left atrial isomerism) [1]. Acquired postoperative AV block is thought to result from damage to the compact AV node or bundle of His and may be transient or permanent. The surgical procedures most commonly associated with the onset of complete AV block include repair of atrioventricular septal defect (AVSD), closure of VSD, resection of obstructive subaortic tissue, and interventions in patients with congenitally corrected transposition [2]. In children, reported incidences of surgical AV block are as high as 2–4%. Normal conduction eventually recovers in more than 60% of patients, usually within the first 10 postoperative days [3,4]. Acute treatment includes temporary pacing (either AV sequential pacing or ventricular pacing only). If the rate of the junctional escape rhythm is high enough to support stable hemodynamics,
temporary pacing can be set as a backup with close monitoring of the underlying rhythm. Important considerations in patients with surgical AV block include careful surveillance for the return of AV conduction and frequent evaluation of temporary pacing wire thresholds. The ventricular output of the temporary pacemaker should be set well above the capture threshold to increase the margin of safety (please refer to the section on temporary pacing). Permanent cardiac pacing is generally indicated in patients who have not recovered from complete AV block within 10–14 days after surgical intervention. A small minority of patients have late recovery of their native AV nodal conduction after surgically acquired complete AV block [3,4].

When providing anesthetic care to a patient with complete AV block and no implanted pacemaker, the following should be considered:

- **Drugs and resuscitation equipment.** Immediate availability of emergency agents such as isoproterenol and epinephrine, in addition to resuscitation equipment, is essential.
- **Transcutaneous cardiac pacing.** Equipment (pacing pads and unit) should be available in case extracardiac pacing becomes necessary. Placing the pacing pads before anesthetic induction may be prudent.
- **Access to temporary transvenous pacing.** Although insertion of a temporary pacing catheter before anesthetic care has been suggested in children with complete AV block, a retrospective study of this approach showed that using it routinely had no benefit [5].

### Supraventricular arrhythmias

#### Premature atrial contractions

Isolated premature atrial contractions (PACs) are relatively common in infants and small children. The early P waves frequently have an abnormal axis and morphology and are typically followed by a normal QRS complex. Atrial bigeminy is characterized by a PAC that follows every sinus beat (Figure 18.5). On occasion, the PACs block at the AV node or conduct aberrantly, displaying an abnormally wide QRS. Blocked PACs can mimic bradycardia, and aberrantly conducted PACs can resemble ventricular ectopy. Most PACs are benign, requiring no therapy. Investigation may be warranted in cases of symptomatic, frequent, or complex (multifocal) PACs. This type of rhythm can be the result of irritation from a central venous catheter or other type of intracardiac line. Radiographic or echocardiographic assessment of catheter/wire tip
position should be considered, because appropriate adjustments can eliminate the atrial ectopy.

**Supraventricular tachycardia**

Supraventricular tachycardia (SVT) is the most common clinically significant arrhythmia in infants and children. This rhythm disturbance is characterized by a narrow or “usual” complex QRS morphology and can occur in structurally normal hearts, as well as in various forms of CHD. “Usual” complex describes a QRS morphology in tachycardia similar to that seen during normal sinus rhythm. This is important because patients with CHD often have abnormalities on their baseline ECG, including a bundle branch block pattern. On occasion, widening of the QRS duration in SVT can be due to aberrancy in the right or left bundle branches or to the tachycardia mechanism itself (i.e., antidromic SVT; refer to the discussion later in this chapter). When the QRS complex is wide, distinguishing between supraventricular and ventricular tachycardia can be challenging.

Two general categories of SVT are recognized: automatic and reentrant. These can be differentiated by evaluating characteristics of the tachycardia (Table 18.1). The most common mechanisms of SVT and their ECG features are noted in Table 18.2. Evaluation of a tachyarrhythmia usually includes a surface 15-lead ECG and a continuous rhythm strip to document onset, termination, and response to medications (e.g., adenosine) or pacing maneuvers. Strips obtained from bedside or transport monitors are helpful for determining tachycardia rate but are usually not sufficient for definitive diagnosis or to distinguish among tachycardia mechanisms.

**Atrial electrogram**

In the postoperative patient, an atrial electrogram (AEG) can be useful in both diagnosis and management of rhythm problems. This type of ECG recording is obtained from the temporary atrial wires placed toward the end of surgery (Figure 18.6). Typically, atrial wires emerge on the right side of the chest wall and ventricular wires on the left, although this configuration may vary. Although both a standard 15-lead ECG and an AEG record the same electrical cardiac activity, these electrical sequences display distinctly different configurations in different leads. On an AEG, the P waves are larger in amplitude, making them easily recognizable because the recording is obtained from wires attached directly to the atrial myocardium. Therefore, in situations in which P waves are not clearly identified on a surface ECG, an AEG may assist in defining atrial activity and the relationship between atrial and ventricular depolarization (Figure 18.7). Such recordings can help clinicians to differentiate between atrial and junctional arrhythmias [6]. For example, during
Table 18.1 Characteristics of supraventricular tachycardia mechanisms

<table>
<thead>
<tr>
<th>Features of the tachycardia</th>
<th>Automatic</th>
<th>Reentrant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset and termination</td>
<td>“Warm-up” at initiation, “cool-down” at termination</td>
<td>Abrupt</td>
</tr>
<tr>
<td>Mode of initiation</td>
<td>Spontaneous</td>
<td>Premature beats</td>
</tr>
<tr>
<td>Ability to initiate/terminate with timed premature beats</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Variation in tachycardia rate</td>
<td>Wide</td>
<td>Narrow</td>
</tr>
<tr>
<td>Response to catecholamines</td>
<td>Increased rate</td>
<td>None or slight rate increase</td>
</tr>
<tr>
<td>Response to adenosine</td>
<td>None</td>
<td>Termination</td>
</tr>
<tr>
<td>Response to drugs that increase refractoriness</td>
<td>Variable</td>
<td>Slowing or termination</td>
</tr>
<tr>
<td>Response to overdrive pacing</td>
<td>Transient suppression, quick resumption</td>
<td>Termination</td>
</tr>
<tr>
<td>Response to cardioversion</td>
<td>None</td>
<td>Termination</td>
</tr>
</tbody>
</table>

Table 18.2 Mechanisms and electrocardiographic features of supraventricular tachycardia

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Electrocardiographic features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Automatic tachycardias</strong></td>
<td></td>
</tr>
<tr>
<td>Ectopic atrial tachycardia or atrial ectopic tachycardia</td>
<td>Atrial rates of 90–330 bpm Incessant rhythm From atrial focus distinct from sinus node Abnormal P-wave morphology and/or axis Distinct P waves preceding QRS complexes No influence of AV block on tachycardia</td>
</tr>
<tr>
<td>Junctional ectopic tachycardia</td>
<td>Narrow QRS tachycardia Incessant rhythm AV dissociation (often) Atrial rate slower than ventricular rate Capture beats frequently seen (QRS complexes slightly earlier than expected from antegrade conduction of normal sinus impulses)</td>
</tr>
<tr>
<td><strong>Reentrant tachycardias</strong></td>
<td></td>
</tr>
<tr>
<td>Atrial flutter</td>
<td>Sawtooth pattern or more discrete undulating P waves (leads II, III, aVF) Variable rates of AV conduction seen (1:1, 2:1, 3:1, or 4:1)</td>
</tr>
<tr>
<td>Atrioventricular reentrant tachycardia (accessory pathway-mediated from concealed bypass tract or Wolff-Parkinson-White syndrome)</td>
<td>P waves immediately following the QRS complex, on ST segment or T wave AV block results in termination of tachycardia</td>
</tr>
<tr>
<td>Atrioventricular nodal reentry tachycardia</td>
<td>P waves buried within QRS and not discernible AV block results in termination of tachycardia</td>
</tr>
</tbody>
</table>

AV, atrioventricular.

Junctional tachycardia, the AEG displays P waves that are either superimposed on the R waves or dissociated from them. In most reentrant SVTs, the PR interval is longer than the RP interval, whereas in sinus rhythm, the PR interval is shorter than the RP interval. An AEG is also helpful in defining the type of an AV block if present and can facilitate the differential diagnosis of sinus node dysfunction vs. various degrees of AV block.

Atrial electrograms can be obtained from bedside monitors (Figure 18.6) or standard 15-lead ECG machines [7]. With a bedside or operating room monitor, it is best to use a rhythm strip with two or more channels so that AEG and ECG recordings can be viewed simultaneously. There are various ways to obtain an AEG along with a standard tracing, depending on various equipment-related factors (e.g., the recorder, epicardial wires, lead configuration).
Figure 18.6 Procedure to obtain an atrial electrogram. Setup for recording an atrial electrogram by using a bedside (or operating room) monitor and a double alligator clamp to connect the atrial temporary pacing wire to the chest (C) or V lead (brown-colored). Alternate lead configurations may be used as described in the text to obtain equivalent tracings. (Source: Miller & Drew [7]. Reproduced with permission of American Association Of Critical-Care Nurses.)

Figure 18.7 Atrial electrogram. Full electrocardiographic tracing with an atrial electrogram in lead V1. Note the easily discernible P waves in the atrial electrogram, which confirm that the rhythm is that of atrial flutter with 2:1 conduction.
The following methods of obtaining an AEG assume the use of a standard 15-lead ECG machine:

- If two atrial wires are present, each lead is attached to the connectors that usually correspond to the right and left arm leads (an alligator clip can be used, if necessary). This allows for a bipolar AEG (large deflection of atrial depolarization with trivial or no signal representative of ventricular activity) to be recorded in lead I. The chest (precordial) leads provide ECG standard tracings. By evaluating the atrial activity as displayed by the AEG (lead I) and the ventricular impulses represented by the QRS complexes on the chest leads (V1–V6), the electrical sequence of cardiac events can be assessed.

- If only a single atrial lead is available, this can be attached to one of the chest leads to obtain a corresponding AEG. In this case, the limb leads can be used to provide a reference for the ventricular activity.

- An alternate lead configuration may utilize a single atrial lead and a skin lead as a substitute for the arm leads to obtain an atrial tracing in lead I, and other leads serve as a reference. A rhythm strip should be printed out so that the recordings can be examined.

In addition to assisting in arrhythmia diagnosis and the selection of appropriate treatment, temporary atrial wires can be used for rapid atrial pacing in attempts to terminate SVT due to reentrant mechanisms or to overdrive suppress an automatic focus.

General management principles for SVT

Management of SVT depends on the clinical status of the patient, the type of tachycardia, and the precise electrophysiologic mechanism that is causing it (Table 18.3). If the tachyarrhythmia is associated with significant hemodynamic compromise, emergent therapy is indicated. Synchronized direct-current cardioversion (0.5–1.0J/kg) should be considered for any acute tachyarrhythmia associated with low cardiac output, recognizing that this approach does not always restore normal sinus rhythm.

Atrial tachycardias

Automaticity of atrial tissue accounts for the majority of supraventricular arrhythmias in this group [8]. In general, these rhythm disorders are more recalcitrant and difficult to treat than reentrant ones.

Focal atrial tachycardia

Focal atrial tachycardia (AT) originates from a single focus in the atrium outside of the sinus node. In the past, this rhythm disturbance was thought to be due solely to enhanced automaticity. Thus, it was often referred to as an automatic or ectopic AT (EAT; also known as atrial ectopic tachycardia, or AET). In rare cases, however, focal AT is triggered or microreentrant in origin and is not due to a true ectopic focus. These forms of AT cannot be easily differentiated on the basis of the surface ECG alone. The clinical characteristics of EAT follow those outlined in Table 18.1 for automatic tachycardias. EAT may be incessant or episodic. The diagnosis is made by identifying abnormal P-wave morphology, axis, or both on a surface ECG or rhythm strips (Figure 18.8). Also, the PR interval may differ from that in sinus rhythm. Atrial rates in EAT are faster than usual sinus rates for the age and physiologic state of the patient. If the atrial rates are very rapid, some of the atrial impulses may not be conducted to the ventricles because of AV node refractoriness.

Ectopic AT is relatively rare and is generally found in two different clinical scenarios [9,10]. A child with a structurally normal heart can develop EAT as a primary phenomenon. In older children, EAT can be incessant and, on rare occasion, lead to the development of ventricular systolic impairment or result in dilated cardiomyopathy due to the chronicity of the tachycardia. In neonates and infants, EAT often follows a more benign course and frequently resolves spontaneously early in life. A patient with CHD can also develop EAT in the postoperative period after cardiac surgery. In such cases, EAT tends to be episodic and transient, usually resolving within days. It has been reported that postoperative patients who developed EAT tended to have a lower preoperative oxyhemoglobin saturation, increased inotropic support both pre- and postoperatively, and a previous atrial septostomy [11]. No specific cardiac repair has been associated with the development of EAT.

Management principles for postoperative EAT

- General considerations. The management of postoperative EAT includes the treatment of fever if present, adequate sedation, correction of electrolyte abnormalities, and the withdrawal of medications that cause sympathetic stimulation (e.g., inotropic agents) or have vagolytic properties (e.g., pancuronium).

- Anti-arrhythmic therapy. The institution of pharmacologic treatment is based on overall heart rate, the duration of the tachycardia, and the hemodynamic status of the patient. Treatment relies on clinical judgment and is influenced by ventricular function. There are no large studies on anti-arrhythmic drug efficacy in postoperative EAT. Medications such as esmolol, procainamide, and amiodarone can be effective in slowing the tachycardia rate [12]. Oral agents (class I, II, and III drugs) can also be of benefit. Digoxin has a minimal effect on the atrial focus, but can decrease the ventricular response by slowing AV conduction [13].

- Ablation therapy. In a very few postoperative patients, EAT can be incessant and life-threatening, and consideration should be given to transcatheter ablation of the atrial focus [14]. It has been reported that propofol anesthesia may not be appropriate for children undergoing catheter ablation of EAT, because administering this drug may terminate the tachycardia and prevent it from being induced by isoproterenol infusion (see Chapter 29) [15].

- Other modalities. Atrial pacing and cardioversion are unlikely to resolve EAT.
### Table 18.3  Acute therapy of perioperative arrhythmias without evidence of hemodynamic compromise

<table>
<thead>
<tr>
<th>Rhythm disturbance</th>
<th>Treatment considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinus bradycardia</td>
<td>See Box 18.1</td>
</tr>
<tr>
<td>Sinus tachycardia</td>
<td>Correct underlying cause</td>
</tr>
<tr>
<td>Premature atrial contractions</td>
<td>Evaluate position of central venous line or intracardiac catheter</td>
</tr>
<tr>
<td></td>
<td>Assess/correct electrolyte disturbances (e.g., hypokalemia)</td>
</tr>
<tr>
<td>Focal (ectopic) atrial tachycardia or atrial ectopic tachycardia</td>
<td>Correct fever, electrolyte abnormalities</td>
</tr>
<tr>
<td></td>
<td>Adequate sedation</td>
</tr>
<tr>
<td></td>
<td>Consider potential detrimental role of inotropes/vagolytics</td>
</tr>
<tr>
<td></td>
<td>ß-blockers – use with caution if depressed cardiac function</td>
</tr>
<tr>
<td></td>
<td>Digoxin</td>
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<tr>
<td></td>
<td>Procainamide</td>
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<td>Amiodarone</td>
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<td></td>
<td>Sotalol</td>
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<td></td>
<td>Flecainide</td>
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<tr>
<td></td>
<td>Propafenone</td>
</tr>
<tr>
<td>Multifocal (chaotic) atrial tachycardia</td>
<td>As in ectopic atrial tachycardia</td>
</tr>
<tr>
<td>Accelerated junctional rhythm</td>
<td>Goals are rate control and decreased automaticity</td>
</tr>
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<td>Junctional ectopic tachycardia (JET)</td>
<td>Correct fever and electrolyte abnormalities</td>
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<td>Consider potential detrimental role of inotropes/vagolytics</td>
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<td>Surface cooling to 34–35°C</td>
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<td>Temporary atrial pacing (for JET rates &lt; 180 bpm)</td>
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<td>Amiodarone</td>
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<td>Hypothermia plus procainamide</td>
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<td>Atrial flutter</td>
<td>Adenosine to confirm diagnosis</td>
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<td>Atrial overdrive pacing</td>
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<td>Atrial fibrillation</td>
<td>Digoxin (except in Wolff–Parkinson–White syndrome)</td>
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<td>Atrioventricular reentrant tachycardia or atrioventricular nodal reentrant tachycardia</td>
<td>Consider vagal maneuvers</td>
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<td>Premature ventricular contractions</td>
<td>Identify and treat underlying cause</td>
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<td>Ventricular fibrillation</td>
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**Multifocal atrial tachycardia**
Multifocal atrial tachycardia (MAT), also known as chaotic atrial rhythm, is an uncommon atrial arrhythmia characterized by multiple (at least three) P-wave morphologies [16]. These different morphologies correspond to multiple foci of automatic atrial activity. Characteristic ECG features include variable PP, RR, and PR intervals and typical atrial rates that exceed 100 bpm. MAT can be seen in young infants without structural heart disease, in postoperative CHD patients, and in children with non-cardiac medical conditions [17,18]. Treatment focuses on ventricular rate control or decreasing automaticity, or both. Drugs such as digoxin, procainamide, flecainide, amiodarone, and propafenone have been found to be successful in converting MAT to sinus rhythm in children [19]. Adenosine, pacing, and direct-current cardioversion are usually ineffective.

**Junctional tachycardias**
Automaticity of junctional tissue accounts for the majority of supraventricular arrhythmias in this group [8]. These rhythm disorders tend to be somewhat resistant to standard pharmacological therapy.

**Accelerated junctional rhythm**
Accelerated junctional rhythm is an arrhythmia that arises from the AV junction. Characteristics of this automatic rhythm include a narrow or “usual” QRS pattern with no preceding P wave. There is either VA dissociation, with ventricular rates faster than atrial rates, or the presence of 1:1 VA conduction retrograde via the AV node. Temporary atrial pacing at a rate 10–20 bpm faster than the junctional rate often re-establishes AV synchrony and effectively suppresses the automatic junctional rhythm. Changes in the patient’s physiologic state (including fever), chronotropic agents, and endogenous catecholamines can stimulate the automatic junctional focus, increasing junctional rates. This rhythm is usually well tolerated and is easily managed with temporary pacing and control of the patient’s underlying physiologic state.

**Junctional ectopic tachycardia**
Junctional ectopic tachycardia (JET) is another automatic rhythm that arises from the AV junction. It is a narrow or “usual” complex tachycardia without preceding P waves. It is distinguishable from accelerated junctional rhythm on the basis of the patient’s heart rate and hemodynamic status. This tachyarrhythmia has been classically defined by heart rates above 160 or 170 bpm with resultant hemodynamic compromise [20]. The diagnosis of JET has also been considered if the junctional rate exceeds the 95th percentile of heart rate for age [21]. There is either VA dissociation with ventricular rates faster than atrial rates or the presence of 1:1 VA conduction (Figure 18.9). If 1:1 VA conduction is identified, a trial of adenosine or rapid atrial pacing may be beneficial to differentiate JET from other reentrant forms of SVT on an AEG.

This type of tachycardia typically occurs in the immediate postoperative period and usually results in hemodynamic instability and significant morbidity, and may contribute to mortality [22–24]. It occurs most commonly after surgical intervention for tetralogy of Fallot, VSD, AVSD, transposition of the great arteries, and total anomalous pulmonary venous return [25]. Other
risk factors for the development of JET are long ischemic cross-clamp and cardiopulmonary bypass times, young age, and a need for inotropic support [26,27]. Excessive retraction of tissues to allow for intracardiac surgical exposure anecdotally has also been linked to JET.

Management principles for postoperative JET
Numerous therapies have been advocated for JET [22,23,27,28]. Strategies for acute care include the following:

- **General considerations.** Core temperature cooling (to 33–35°C) in the younger patient by the use of cooling blankets, fans, or cold compresses has been shown to be of benefit in reducing the tachycardia rate [29–31]. Shivering, if significant, should be minimized to prevent potentially detrimental increases in oxygen consumption. Additional suggested approaches include withdrawing or decreasing vagolytic agents and any medications associated with catecholamine stimulation, and correcting abnormal levels of electrolytes, especially magnesium, potassium, and calcium.

- **Atrial pacing.** Temporary atrial pacing at heart rates 10–20 bpm above the JET rate establishes AV synchrony and often improves hemodynamics. However, if the JET rate is faster than 180 or 190 bpm, overdrive atrial pacing often confers little benefit.

- **Anti-arrhythmic medications.** The two most widely used drugs for JET are amiodarone and procainamide [27,28,32–34]. Amiodarone has a longer onset of action and a longer half-life than procainamide. The drug has been shown to reduce the heart rate in JET patients during the initial bolus infusion [33,34]. Core cooling is often continued but is not generally needed for efficacy. Administering amiodarone may be a way to avoid having to evaluate clinical signs reflecting the adequacy of cardiac output (distal peripheral perfusion, skin temperature) in a patient with hypothermia and tachycardia. Amiodarone does not directly influence ventricular function and is generally thought to cause less likelihood of hypotension during the initial bolus infusion than procainamide does. However, the drug should be administered with caution, given its potential adverse events (hypotension, bradycardia, AV block). The benefits of procainamide are that it has a faster onset of action and a shorter half-life than amiodarone. However, procainamide appears to be effective mainly when used with core cooling. It may also cause a decrease in systemic vascular resistance, with resultant hypotension, particularly during bolus infusions. Procainamide can also have negative inotropic properties. Usually, a fluid bolus or other volume expander should be given before or during procainamide therapy to maintain adequate hemodynamics. Both amiodarone and procainamide have been shown to be effective in the treatment of JET in published retrospective studies; however, the main determinant of drug selection in clinical practice is influenced by physician/institutional preference. Because amiodarone and procainamide can each cause QT prolongation and proarrhythmic

![Junctional ectopic tachycardia](image.png)
side-effects, these two drugs should not be administered concomitantly. Anecdotal evidence suggests that digoxin loading can slow the JET rate, but this has not been well documented in the literature. β-blockers and calcium-channel blockers can depress myocardial contractility, a feature that may limit their use in the immediate postoperative period. In this regard, a short-acting agent such as esmolol may offer a larger margin of safety. The use of intravenous (IV) class IC agents such as propafenone and flecainide has been reported, but these drugs have not been studied extensively for JET [35–37]. The natural history of perioperative JET is that it resolves within 2–5 days after the surgical intervention. Long-term anti-arrhythmic therapy is usually not necessary. Rarely, extracorporeal membrane oxygenator (ECMO) support may be necessary for incessant hemodynamically significant JET not responding to other therapies.

- **Cardioversion** is generally considered ineffective in terminating JET.
- **Catheter ablation** of the junctional focus should be considered only as a last resort, because it can result in complete AV block, given that postoperative JET is usually transient [38,39].

**Reentrant supraventricular tachycardias**

Reentry, also known as “circus” movement or reciprocation, implies that a single stimulus or excitation wavefront returns and reactivates the same site or tissue from which it originated. Reentrant forms of SVT may or may not involve accessory pathways.

**Atrial flutter**

Atrial flutter is a rhythm disturbance confined to the atrial myocardium. The electrophysiologic basis for this arrhythmia involves reentry within the atrium itself. The typical or classic form of atrial flutter is characterized by a negative sawtooth P-wave pattern and atrial rates that exceed 300 bpm (Figure 18.10). This form of atrial flutter is occasionally seen in otherwise healthy neonates but is relatively uncommon in children. In patients with CHD, slower atrial rates and varying P-wave morphologies are more frequently seen than in those without CHD. This is due to anatomic abnormalities related to suture lines, scars, or fibrosis from previous surgery involving atrial tissue. This form of “scar flutter” is commonly termed intra-atrial reentrant tachycardia (IART) [40]. It is one of the most common arrhythmias in postoperative patients with structural heart disease, and is considered the cause of significant morbidity after certain types of surgical interventions [41]. Procedures that involve extensive atrial suture lines, such as atrial redirection procedures (Senning or Mustard operations) and those associated with atrial dilation (Fontan surgery) pose a particularly high risk of atrial flutter. The possibility of atrial flutter is suggested by abrupt onset of a rapid atrial rhythm that remains relatively regular over time. AV nodal conduction accounts for variability in the ventricular response rate. Rapid clinical deterioration is likely; fast ventricular rates frequently require prompt intervention.

**Management principles for atrial flutter**

- Adenosine will not terminate tachycardia but may assist in confirming the diagnosis by uncovering flutter waves during AV block.
• **Atrial overdrive pacing** is a safe and effective way to rapidly terminate atrial flutter by using a transesophageal or transvenous pacing catheter or epicardial wires [42]. After the atrial cycle length is assessed, rapid atrial stimulation is performed in short bursts to attempt interruption of the reentry circuit.

• **Synchronized cardioversion** is the treatment of choice in any patient with unstable hemodynamics. Placement of the cardioversion pads over the front and back of the hemithorax may be necessary to provide a shock vector through the entire atrium, which is usually thickened in patients with CHD.

• **Pharmacologic agents** such as digoxin, procainamide, and amiodarone can be used in urgent situations. Drugs for controlling the ventricular response in atrial flutter include β-blockers and calcium-channel blockers. Important considerations regarding drug selection are patient age, underlying ventricular function, and whether there is sinus node dysfunction (a concomitant problem in patients with recurrent atrial flutter). Ibutilide and sotalol are available for rapid termination of atrial flutter and have been used in postoperative adult patients with CHD [43].

• **Long-term drug therapy** is frequently necessary in patients with CHD because of the potential for recurrence and associated rapid AV conduction.

• **Pacemaker therapy**, atrial anti-tachycardia pacing, and radiofrequency ablation are additional modalities often used for long-term management.

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**Atrial fibrillation**

Atrial fibrillation is a complex arrhythmia that can be due to either multiple reentrant circuits or focal points within the pulmonary veins. In the majority of cases, it originates in the left atrium (in contrast to atrial flutter, which is generally considered a disease of the right atrium). In children, this tachyarrhythmia is less frequent than atrial flutter. The atrial rates are rapid and irregular, ranging from 400 to 700 bpm. Ventricular response rates are variable but generally range between 80 and 150 bpm. Patients at potential risk for atrial fibrillation include those with an enlarged left atrium (e.g., rheumatic heart disease, severe AV valve regurgitation), pre-excitation syndromes, structural heart disease (Ebstein anomaly, tricuspid atresia, ASDs), and cardiomyopathies.

**Management principles for atrial fibrillation**

• Management principles are similar to those for atrial flutter except that atrial overdrive pacing is not effective in terminating the arrhythmia.

• **Cardioversion** is more likely to be required, and higher amounts of energy may be needed. As in the case of atrial flutter, placement of cardioversion pads should be optimized by using a front and back configuration over the chest. Anticoagulation and consideration of transesophageal echocardiography for evaluating intracardiac thrombi are recommended before cardioversion if atrial fibrillation has been present more than 48 hours [44,45].

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**Atrioventricular reentrant tachycardia and atrioventricular nodal reentrant tachycardia**

Atrioventricular reentrant tachycardia (AVRT) is the most common type of SVT in infancy and childhood. It is mediated by an accessory pathway between the atrium and ventricle. The tachycardia circuit typically consists of conduction from the atrium, down the AV node, through the bundle of His and ventricles, and then up the accessory
connection back to the atrium. This form of SVT is referred to as orthodromic SVT and occurs in patients with Wolff–Parkinson–White syndrome (WPW; Figure 18.11), concealed accessory pathways, and permanent junctional reciprocating tachycardia. In contrast, in antidromic SVT, conduction travels from the atrium, down the accessory connection, through the ventricles, up the AV node, and back to the atrium. The QRS complex in this form of SVT is wide. Antidromic tachycardia can occur in patients with WPW and other pre-excitation variants (Mahaim tachycardia).

Atrioventricular nodal reentrant tachycardia (AVNRT), or reentry within the AV node, is most likely in the adolescent or young adult. In AVNRT, the AV node has two physiologically distinct components, designated the “slow” and “fast” AV nodal pathways. The typical form of AVNRT consists of antegrade conduction (from the atrium to the ventricle) via the slow pathway, followed by retrograde conduction (back to the atrium) via the fast pathway.

Both AVRT and AVNRT have clinical characteristics typical of reentrant tachycardia mechanisms as listed in Table 18.1. The two can often be distinguished by closely evaluating the surface ECG during sinus rhythm and tachycardia. In orthodromic AVRT, the P wave can be seen immediately after the QRS complex or in the ST segment or T wave (Figure 18.12). The reason for this P-wave location is that a set time period is necessary for conduction to proceed from the ventricles through the accessory pathway back to the atrium. In contrast, in AVNRT, the P wave is buried in the QRS complex and is often not discernible (Figure 18.13). This is the case because the tachycardia circuit is within the AV node, and the atria and the ventricles are activated almost simultaneously. Patients with structurally normal hearts, as well as those with CHD, can have either AVRT or AVNRT. Ebstein malformation of the tricuspid valve is frequently associated with AVRT secondary to one or multiple accessory pathways. The accessory connections in this condition are usually right-sided. Congenitally corrected transposition can be associated with an Ebsteinoid left-sided AV valve, and left-sided accessory pathways can be identified in a subset of patients.

Management principles for AVRT or AVNRT
- **Direct current synchronized cardioversion** (0.5–1.0J/kg) should be performed in hemodynamically unstable patients. A lower energy setting is adequate if paddles are used directly on the heart (epicardial paddles). Cardioversion should also be considered in stable patients when potential rapid clinical deterioration is anticipated or after unsuccessful conventional therapy.
- In stable patients, tachycardia can be rapidly terminated with **vagal maneuvers** (Valsalva maneuver, coughing, gag reflex stimulation, ice to the face, Trendelenburg position), which enhance parasympathetic influences.[46]
- **Adenosine** is the first-line drug therapy for SVT[47–49]. Other agents (digoxin, edrophonium, β-blockers, calcium-channel blockers, phenylephrine, dexmedetomidine) have been used in acute treatment with variable results; however, serious adverse effects can be seen. Continuous ECG monitoring is recommended, as well as ensuring that atropine and other emergency drugs are available, because transient bradycardia may follow tachycardia termination (Figure 18.14). During short-term pharmacologic therapy, backup pacing may

Figure 18.12 Atrioventricular reentrant tachycardia. Electrocardiogram showing a narrow-complex tachycardia with a regular rate and a distinct retrograde P wave approximately 80 ms after the QRS complex.
be appropriate, depending on the drug and clinical status of the patient.

- **Rapid atrial pacing** can be performed with a trans-esophageal electrode catheter or via temporary atrial pacing wires. Beforehand, one must ensure that there is no ventricular capture by the catheter or temporary wires at the desired output site. Rapid atrial pacing is performed by pacing the atrium at 10–20% faster than the SVT rate for a period of up to 15 seconds, which typically terminates the tachycardia. In the patient with a high catecholamine state, SVT can be successfully terminated, but rapid recurrence is possible. In this case, a higher level of patient sedation and limiting catecholamine stimulation should be considered.
• Anti-arrhythmic medication can be instituted once the tachycardia has terminated or if it terminates and then reinitiates. For perioperative patients unable to take oral medications, parenteral therapy may include procainamide or amiodarone. β-blockers and calcium-channel blockers may be less desirable in such cases because of their negative effects on myocardial contractility; a short-acting agent, such as esmolol, may offer a larger margin of safety.

• Transcatheter ablation may be warranted in patients with a history of SVT who would prefer not to take medications, or in those with incessant tachycardia that cannot be controlled with medications. Success rates for transcatheter ablation exceed 95%.

KEY POINTS: SUPRAVENTRICULAR ARRHYTHMIAS

• Premature atrial contractions can be due to irritability from an intracardiac wire/catheter, therefore, tip position should be evaluated

• SVT is the most common clinically significant arrhythmia in the pediatric age group; it is characterized by a narrow or “usual” complex QRS morphology

• Supraventricular tachyarrhythmias are categorized into automatic and reentrant types; these can be differentiated by evaluating features of the tachycardia

• Atrial electrograms facilitate the diagnostic assessment of tachyarrhythmias and can be obtained using bedside/operating room monitors or full ECG recordings

• The management of postoperative JET includes consideration of overdrive temporary atrial pacing to restore AV synchrony, sedation, mild hypothermia, and drugs

• Any acute rhythm disturbance requires prompt evaluation of hemodynamics

• In the stable patient, vagal maneuvers, drug therapy, and rapid atrial pacing may be considered to terminate a supraventricular arrhythmia

• Synchronized cardioversion is first line therapy for unstable reentrant supraventricular arrhythmias

• A wide QRS tachycardia should always be considered of ventricular origin until proven otherwise

Ventricular arrhythmias

Ventricular arrhythmias are rhythm disorders that arise distal to the bifurcation of the common His bundle. These are relatively rare in young children and are more common in patients with underlying genetically abnormal cardiac sodium or potassium channels and in adolescents or young adults with previously operated CHD. Patients with ventricular rhythm abnormalities may have few or no symptoms, or they may be gravely ill. Evaluation should include reviewing the medical history for findings suggestive of associated cardiovascular pathology or potential cause of the arrhythmia, analyzing the ECG, and, most importantly, assessing hemodynamic state.

Premature ventricular contractions

Premature ventricular contractions (PVCs) are premature beats that originate in the ventricular myocardium. These are characterized by: premature QRS complexes not preceded by premature atrial activity; a QRS morphology that differs from that in sinus rhythm; a long QRS duration for the patient’s age (a frequent but not universal finding); and abnormalities of repolarization. In patients with a structurally normal heart, PVCs of a single QRS morphology (uniform) without associated symptoms are generally considered benign. Premature ventricular contractions that merit further investigation include those that have multiple morphologies (multiform) on ECG, occur with moderate frequency, and are associated with symptoms or occur in a patient with an abnormal heart.

Ventricular ectopy in the perioperative period can be secondary to myocardial irritation from intracardiac catheters or direct surgical stimulation. Additional causes include respiratory (hypoxemia), electrolyte (hypokalemia), and metabolic derangements (acidosis). Isolated PVCs can also be due to pharmacologic agents (e.g., recreational drugs), myocardial injury, poor hemodynamics, and prior complex surgical intervention.

Ventricular tachycardia

Ventricular tachycardia (VT) is defined as three or more consecutive ventricular beats occurring at a rate greater than 120 bpm in adults, or more than 20% greater than the preceding sinus rate. The QRS morphology in VT is different from that in sinus rhythm and is usually wide for the patient’s age. Electrocardiographic features that support this diagnosis include AV dissociation; intermittent fusion (i.e., a QRS complex of intermediate morphology occurring between two other QRSs with distinctly different morphologies); QRS morphology of VT similar to that of isolated PVCs; and tachycardia rate in children usually below 250 bpm. An RBBB QRS morphology is most common in infants with VT, whereas in older children, an LBBB pattern is more frequent with wider QRS morphologies.

Various qualifiers have been proposed to further characterize VT. The classification of VTs as monomorphic (one QRS morphology) or polymorphic (multiple QRS morphologies) is based on the evaluation of the QRS pattern in multiple ECG leads. VT is considered to be sustained or non-sustained if it lasts more or less than 30 seconds, respectively.

Acute onset of VT in pediatric patients may be due to hypoxia, acidosis, electrolyte imbalance, or metabolic problems. In the perioperative or immediate postoperative setting, the onset of VT can suggest myocardial ischemia or coronary artery injury, or both. This arrhythmia can
also occur in patients with depressed myocardial function, poor hemodynamics, prior surgical interventions, myocardial tumors, cardiomyopathies (hypertrophic, dilated, left ventricular non-compaction, arrhythmogenic right ventricular dysplasia), myocarditis, acute injury (trauma), and primary sodium or potassium channel abnormalities (long QT syndrome, Brugada syndrome; see sections that follow). Among patients with CHD and ventricular arrhythmias, those at higher risk include older patients who have undergone tetralogy of Fallot repair and individuals with significant residual hemodynamic abnormalities. In patients with structural heart disease, the following potential causes of ventricular ectopy have been proposed: inadequate myocardial protection during the surgical procedure, chronic pressure or volume loads, residual or recurrent pathology, and scar formation at the ventriculotomy site.

Monomorphic VT

Although occasionally seen in patients with otherwise normal hearts, monomorphic VT is more common in those with underlying cardiac abnormalities. In the abnormal heart, the tachycardia is thought to originate from a reentrant focus in scarred or damaged myocardial tissue. The ECG findings include a wide regular QRS rhythm of uniform morphology (Figure 18.15).

Polymorphic VT

**Torsades de pointes**

Torsades de pointes, or torsades (“twisting of the peaks”), refers to a form of polymorphic VT. The characteristic ECG feature is a varying QRS morphology manifested as positive and negative oscillations of the QRS direction that twists around an isoelectric baseline (Figure 18.16). Polymorphic VT may occur in long QT syndromes, can
be secondary to drug therapy or neurologic pathology, or be the result of myocardial ischemia. Torsades may terminate spontaneously or degenerate into ventricular fibrillation (VF).

Long QT syndromes
Long QT syndrome (LQTS) is an electrical disturbance that affects ventricular repolarization and predisposes children to arrhythmias such as torsades de pointes, VT, VF, and bradyarrhythmias [50–52]. The disorder is associated with a propensity for syncope, cardiac arrest, and sudden death.

Long QT syndrome can be congenital (inherited) or acquired. The congenital varieties are predominantly the result of genetic defects in the sodium or potassium channels responsible for maintaining electrical homeostasis in the heart. The incidence of LQTS is not clearly known, but it is estimated that one in 5,000 individuals are gene carriers of the congenital form. The autosomal dominant variety, Romano–Ward syndrome, represents the most common form of congenital LQTS. The Jervell and Lange–Nielsen syndrome has an autosomal recessive pattern of inheritance and, in addition to QT prolongation, is characterized by deafness. Genetic testing is commercially available for LQTS-causing defects. Although efforts to develop gene-specific therapy are under way, all patients with LQTS are treated similarly at present.

Suggested clinical diagnostic criteria for LQTS are based on ECG findings, clinical history, and family history [53]. The hallmark of the disorder is prolongation of the corrected QT interval (QTc) on the resting ECG (Figure 18.17). It should be noted, however, that individuals with LQTS may not display the repolarization abnormality manifested as QT interval prolongation. Several equations can be used to determine the QTc, the most common one being Bazett’s formula:

\[
\text{Corrected QT} = \frac{\text{measured QT interval}}{\sqrt{\text{preceding RR interval}}}
\]

A QTc > 0.47 seconds is considered abnormal regardless of the patient’s age.

Management principles in LQTS
- \(\beta\)-adrenergic blockade. An important aspect of perioperative management is ensuring adequate \(\beta\)-adrenergic blockade and minimizing sympathetic stimulation, because this may trigger tachyarrhythmias. Premedication with midazolam can minimize anxiety and pain, which can trigger arrhythmias.
- Perioperative management. Conditions and drugs associated with QT interval prolongation should be avoided [54]. Electrolyte abnormalities (e.g., hypokalemia, hypocalcemia, hypomagnesemia) should be corrected before surgery. Intravenous lidocaine (1.5 mg/kg) given before laryngoscopy and intubation has been shown to prevent QT prolongation that can be seen during the time of airway instrumentation and may be considered [55]. Intraoperative tachyarrhythmias can be treated with additional doses of \(\beta\)-blockers and magnesium. Other beneficial drugs include phenytoin and lidocaine. Although several agents routinely used in anesthetic practice increase the QT interval (IV medications

Figure 18.17 Long QT syndrome. Electrocardiographic recording from a child with long QT syndrome. The corrected QT interval is 0.58 seconds. Note the presence of T-wave alternans (alternating T-wave morphologies), a classic but uncommon finding in patients with long QT syndrome.
and volatile agents), in most cases these drugs are administered without untoward effects. Care should be taken in managing postoperative nausea, because some antiemetics can cause QT prolongation and may increase the risk of arrhythmias. A study in children with LQTS documented an increased risk of adverse events (2.6%) during anesthetic emergence in those who received both neuromuscular blockade reversal drugs (anticholinergic/anticholinesterase medication) and ondansetron. One event was described as torsades and was treated successfully [56]. These observations suggest an increased vulnerability during periods of enhanced sympathetic activity (emergence) and after the administration of drugs associated with QT interval prolongation. A comprehensive list of drugs that prolong the QT interval or may induce torsades can be found in the frequently updated and highly valuable website of The Arizona Center for Education and Research on Therapeutics (http://crediblemeds.org/everyone/composite-list-all-qtdrugs/?rf=US).

• **Postoperative care.** Patients should be closely monitored until they emerge from anesthesia and their QTc returns to preoperative values. Adequate pain control should be provided to minimize adrenergic responses that can trigger arrhythmias.

  Acquired forms of long QT may result from electrolyte disturbances (hypokalemia, hypocalcemia, hypomagnesemia), drug therapy (anti-arrhythmic agents, antipsychotic drugs), and neurologic or endocrine abnormalities. Therapy in such cases should focus on correcting the underlying cause.

General management principles for VT

• A wide QRS tachycardia should always be considered to be of ventricular origin until proven otherwise, although some atypical forms of supraventricular arrhythmias may mimic VT.

• A critical aspect of caring for patients with an acute ventricular rhythm abnormality is promptly evaluating their hemodynamics. In general, sustained ventricular arrhythmias are poorly tolerated and require immediate attention. Unstable patients require cardiopulmonary resuscitation and electrical cardioversion.

• Pharmacological therapy may be indicated in stable patients to treat VT or to prevent its recurrence. Recommended agents include amiodarone, lidocaine, procainamide, and ß-blockers. The choice of agent depends on the associated clinical scenario.

• Electrical cardioversion in torsades de pointes should be performed only if the arrhythmia is sustained. In patients with frequent but non-sustained runs of torsades, cardioversion is of no benefit and may be detrimental. Magnesium sulfate is considered the first-line drug and lidocaine may also have a role in therapy. Procainamide and amiodarone are relatively contraindicated because they can cause QT prolongation.

• Pacing and isoproterenol may be considered for polymorphic VT associated with acquired QT prolongation such as that related to the proarrhythmic effects of certain drugs, particularly in the setting of long pauses in the cardiac cycle.

**Brugada syndrome**

Brugada syndrome is a genetically determined disease characterized by a distinct ECG pattern (RBBB with covered or saddle-shaped ST elevation in leads V1–V3) (Figure 18.18) [57]. Various genetic defects that lead to abnormalities in sodium and calcium currents have been identified in affected patients [58]. The inheritance pattern is usually autosomal dominant, although there is vast genetic heterogeneity. This syndrome has been rarely reported in children [59]. Recent publications show that infants with rapid VT and conduction abnormalities but no cardiac or metabolic abnormalities are likely to have disease-causing mutations in genes for the cardiac depolarizing channels in the Brugada regions [60].

Clinically, the importance of Brugada syndrome is related to its strong propensity for ventricular arrhythmias. It is thought to be responsible for 5–20% of all sudden deaths in people with structurally normal hearts. It is probably underdiagnosed and has a national prevalence of approximately 5 in 10,000 individuals. The ECG features are often concealed or transient. In patients with suspected Brugada syndrome and a normal ECG pattern, administering a sodium-channel blocker can unmask the classic pattern. Anti-arrhythmic medications appear to have limited efficacy in preventing recurrences of ventricular arrhythmias and prolonging survival in Brugada syndrome patients. Only patients with implantable cardioverter-defibrillators (ICDs) appear to be protected from sudden death. From the standpoint of anesthetic care, it is of note that many events in patients with Brugada syndrome occur during rest or sleep, implicating sedation and anesthesia as time of risk. Perioperative considerations also include factors associated with further ST segment elevation potentially leading to arrhythmias (drugs, electrolyte abnormalities, and fever) [61]. An updated list of drugs to be avoided in Brugada syndrome can be found at www.brugadadrugs.org.

**Catecholaminergic polymorphic ventricular tachycardia**

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an inherited cardiac channelopathy characterized by polymorphic VT triggered by adrenergic stimulation. It can be caused by a mutation in the ryanodine receptor gene (RYR2) or in the cardiac calsequestrin gene (CASQ2). It has an incidence of approximately 1 in 10,000. It usually presents as syncope precipitated by exercise, but it can also present as sudden death. Pharmacological therapy is primarily with ß-blockers, particularly nadolol [62]. Studies have also shown some benefits from using flecainide in conjunction with ß-blockade [63,64]. In select patients, the placement of an ICD may be warranted. This form of therapy has to be used judiciously because shocks can trigger an electrical storm secondary to the adrenergic
surge that follows a discharge. Left cervical sympathetic denervation can be considered in patients who are not able to tolerate β-blockers, who have recurrent arrhythmias despite maximal medical therapy, or who meet the criteria for ICD placement but in whom it cannot be placed [65].

**Management principles for CPVT**
- **Adrenergic surges.** Patients undergoing surgical procedures or other interventions associated with a high level of stimulation have special considerations. Extreme care should be taken to minimize adrenergic surges because they can trigger ventricular arrhythmias in such patients. Adequate anxiolysis and pain control should be achieved during any surgical or nonsurgical procedure that may be stimulating.

**Ventricular fibrillation**
Ventricular fibrillation is an uncommon arrhythmia in children. It is characterized by chaotic, asynchronous ventricular depolarizations that fail to generate an effective cardiac output. The ECG in VF shows low-amplitude, irregular deflections without identifiable QRS complexes. A loose ECG electrode may mimic these surface ECG features; therefore, immediate clinical assessment of cardiac output (i.e., checking for a pulse) should be performed and adequate ECG pad contact ensured when VF is suspected.

**Management principles for VF**
- **Immediate defibrillation** (initial dose of 2–4J/kg for the transthoracic approach) is the definitive therapy, because VF is lethal if left untreated. If the first shock is unsuccessful, a second shock should be delivered at double the energy dose. Infant paddles are generally recommended for those weighing less than 10 kg. Adult paddles are suggested for children weighing over 10 kg in order to reduce impedance and maximize current flow.
- **Adequate airway control (oxygenation, ventilation) and chest compressions** should be rapidly instituted during preparation for defibrillation or between shocks if several defibrillation attempts are needed.
- **Adjunctive pharmacologic agents** for VF include amiodarone and lidocaine. The American Heart Association’s current guidelines for cardiopulmonary resuscitation and emergency cardiac care recommend using amiodarone as the first-line anti-arrhythmic drug for shock-refractory, pulseless VT, and VF [66]. Recent studies have shown that lidocaine may better promote the spontaneous return of circulation and 24-hour survival than amiodarone [67].
- **Additional therapies** such as mechanical circulatory support should be considered.
The most widely accepted management strategies for perioperative ventricular rhythm disturbances without associated hemodynamic compromise are summarized in Table 18.3.

**KEY POINTS: VENTRICULAR ARRHYTHMIAS**

- Premature ventricular contractions are generally benign in the structurally normal heart, of uniform QRS morphology, and asymptomatic patient; however, they may also result from myocardial irritation or may be due to other serious causes.
- VT is characterized by QRS morphology that is different than that in sinus rhythm and usually wide.
- VT requires prompt evaluation of hemodynamic status, as it may rapidly convert to ventricular fibrillation, resulting in cardiac arrest.
- In LQTS, perioperative ß-blockade is essential and although caution must be exercised with drugs and conditions that prolong the QT, in most cases anesthetic management is uneventful.
- Ventricular fibrillation requires institution of cardiopulmonary resuscitation and immediate defibrillation; a loose ECG electrode should be excluded.

**Pharmacologic therapy of cardiac arrhythmias**

Anti-arrhythmic drugs exert their effects primarily by blocking sodium, potassium, or calcium channels, or by altering adrenergic tone. These drugs are generally classified according to their presumed mechanism of action and electrophysiologic effects. The well-known drug classification scheme introduced by Vaughan Williams (Table 18.4) and modified over the years is frequently used [68]. Although an oversimplification, this classification may be helpful in predicting response to therapy. Appropriate drug selection requires an understanding of the mechanism of the arrhythmia and the putative effects of the agent. This section discusses pharmacologic therapy for arrhythmias, focusing on the agents most frequently used for acute management in children (Table 18.5) [69]. It is emphasized that perioperative consultation with a specialist should be considered while caring for patients with rhythm disturbances or those receiving chronic anti-arrhythmic therapy as necessary.

**Class I agents**

The largest group of anti-arrhythmic drugs are the sodium-channel blockers. The relatively large size of this class of agents has led to its subclassification into IA, IB, and IC groups on the basis of each drug’s cellular actions. Group IC consists of oral drugs only and is not discussed in this chapter.

**Class IA agents**

The class IA drugs include procainamide, quinidine, and disopyramide. Their predominant electrophysiologic effect is the prolongation of both myocardial repolarization (QT interval) and the action potential. The mechanism of action is primarily related to inhibition of the fast sodium channels. The anticholinergic (vagolytic) properties of these drugs account for their more pronounced effects at fast heart rates.

**Procainamide**

Procainamide is a potent sodium-channel blocker and, to a lesser extent, a potassium-channel blocker. This drug slows atrial conduction (prolongs the PR interval) and lengthens the QRS duration and QT interval. Procainamide is useful in the management of both atrial and ventricular arrhythmias [27,32,70,71]. The suppression of abnormal automaticity accounts for its usefulness in the treatment of EAT, JET, and VT. The drug is generally more effective than lidocaine in acutely terminating sustained VT.

Procainamide can be administered via the oral, IV, or intramuscular routes. For the treatment of acute arrhythmias, IV loading (doses of 10–15 mg/kg) over a period of 30–45 minutes is usually required. The lower end of the loading dose spectrum is suggested for younger patients. Continuous ECG monitoring and frequent blood pressure assessments are recommended during the loading phase. The drug is rapidly distributed after IV injection. After the loading dose is administered, an infusion is frequently initiated at a rate of 30–50 μg/kg/min. Monitoring plasma levels is advisable, and the maintenance infusion rate should be adjusted as needed to achieve therapeutic levels between 4 and 8 μg/mL. The drug is eliminated by the kidneys (50–60%) and through hepatic metabolism (10–30%). Hepatic acetylation generates N-acetylprocainamide (NAPA), a metabolite with anti-arrhythmic (class III) properties.

Potential side-effects of procainamide include hypotension due to blocking of alpha-adrenergic receptors and decreased systemic vascular resistance during rapid IV administration. Significant QT prolongation and proarrrhythmia are also well described. Additional non-therapeutic effects include negative inotropy and AV block. Gastrointestinal symptoms, a lupus-like syndrome, and blood dyscrasias can also occur.

**Class IB agents**

Class IB drugs include lidocaine, mexiletine, phenytoin, and tocainide. These inhibit fast sodium channels and shorten the action potential duration and the refractory period.
### Table 18.4: Classification of anti-arrhythmic agents

<table>
<thead>
<tr>
<th>Class and action</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I: sodium-channel blockers. Drugs may be subclassified into IA, IB, and IC categories</td>
<td></td>
</tr>
<tr>
<td>IA agents – moderately depress phase zero upstroke of the action potential, slow conduction, and prolong repolarization. Effectively slow conduction in atria, ventricles, and accessory connections</td>
<td>Procainamide</td>
</tr>
<tr>
<td></td>
<td>Quinidine</td>
</tr>
<tr>
<td></td>
<td>Disopyramide</td>
</tr>
<tr>
<td>IB agents – shorten action potential duration and result in minimal alteration of conduction. These agents are usually not effective in the treatment of supraventricular tachycardia</td>
<td>Lidocaine</td>
</tr>
<tr>
<td></td>
<td>Mexiletine</td>
</tr>
<tr>
<td></td>
<td>Phenytoin</td>
</tr>
<tr>
<td>IC agents – significantly depress phase zero upstroke, with marked slowing of conduction but little change in refactoriness</td>
<td>Flecainide</td>
</tr>
<tr>
<td></td>
<td>Propafenone</td>
</tr>
<tr>
<td>Class II: β-adrenergic receptor blockers. Anti-arrhythmic effects result from slowing conduction and decreasing automaticity, particularly in the sinoatrial and atrioventricular nodes</td>
<td>Esmolol</td>
</tr>
<tr>
<td></td>
<td>Atenolol</td>
</tr>
<tr>
<td></td>
<td>Metoprolol</td>
</tr>
<tr>
<td></td>
<td>Propranolol</td>
</tr>
<tr>
<td>Class III: potassium-channel blockers. Primarily prolong action potential duration, with resultant prolongation of refactoriness</td>
<td>Amiodarone</td>
</tr>
<tr>
<td></td>
<td>Sotalol</td>
</tr>
<tr>
<td></td>
<td>Bretylum</td>
</tr>
<tr>
<td></td>
<td>Ibutilide</td>
</tr>
<tr>
<td>Class IV: calcium-channel blockers with predominant sites of action in the sinoatrial and atrioventricular nodes.</td>
<td>Verapamil</td>
</tr>
<tr>
<td></td>
<td>Diltiazem</td>
</tr>
<tr>
<td>Others</td>
<td>Atropine</td>
</tr>
<tr>
<td></td>
<td>Digoxin</td>
</tr>
<tr>
<td></td>
<td>Adenosine</td>
</tr>
<tr>
<td></td>
<td>Magnesium sulfate</td>
</tr>
</tbody>
</table>

### Table 18.5: Intravenous anti-arrhythmic agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenosine</td>
<td>100 μg/kg rapid bolus, increase by 50 μg/kg every 2 min, up to 300 μg/kg maximum</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Load 5 mg/kg over 30–60 min</td>
</tr>
<tr>
<td></td>
<td>Infusion 5–10 μg/kg/min</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Load 20–30 μg/kg (divide as 1/2, 1/4, 1/4 every 8 hours), dose is age-dependent</td>
</tr>
<tr>
<td></td>
<td>Maintenance 7–10 μg/kg/day divided every 12 hours orally</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>Load 0.25 mg/kg up to 20 mg bolus over 2 min</td>
</tr>
<tr>
<td></td>
<td>Infusion 0.1–0.3 mg/kg/hour, may increase up to 15 mg/hour</td>
</tr>
<tr>
<td>Esmolol</td>
<td>Load 500 μg/kg over 1–2 min</td>
</tr>
<tr>
<td></td>
<td>Infusion 50 μg/kg/min starting dose, may increase gradually to 400 μg/kg/min</td>
</tr>
<tr>
<td>Flecainide (not available in US)</td>
<td>1–2 mg/kg over 5–10 min</td>
</tr>
<tr>
<td>Magnesium sulfate</td>
<td>25–50 mg/kg (up to 2 g) over 20–30 min</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>Load 1 mg/kg every 5 min up to three times</td>
</tr>
<tr>
<td></td>
<td>Infusion 20–50 μg/kg/min</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>1–3 mg/kg over 10–15 min</td>
</tr>
<tr>
<td>Procainamide</td>
<td>Load 10–15 mg/kg over 30 to 45 min</td>
</tr>
<tr>
<td></td>
<td>Infusion 40–50 μg/kg/min</td>
</tr>
<tr>
<td>Propafenone (not available in US)</td>
<td>Load 1 mg/kg over 10 min</td>
</tr>
<tr>
<td></td>
<td>Infusion 4–7 μg/kg/min</td>
</tr>
<tr>
<td>Propranolol</td>
<td>0.05–0.15 mg/kg over 5 min</td>
</tr>
<tr>
<td>Sotalol (not available in US)</td>
<td>Load 0.2–1.5 mg/kg</td>
</tr>
<tr>
<td>Verapamil</td>
<td>0.05–0.30 mg/kg over 3–5 min, maximum 10 mg, not under 12 months of age</td>
</tr>
</tbody>
</table>
**Lidocaine**

Lidocaine is a short-acting agent with primary effects on ventricular myocardium. It is one of the anti-arrhythmic drugs more commonly used in operating rooms and intensive care units. It is effective for suppressing frequent ventricular ectopy and warning arrhythmias and for preventing the recurrence of VT and VF [72–75].

An initial IV bolus of 1 mg/kg is recommended that can be repeated after several minutes if ineffective. The maintenance infusion rate ranges between 20 and 50 μg/kg/min. Lidocaine is rapidly metabolized in the liver by microsomal enzymes. Therefore, drugs associated with altered microsomal enzyme activity and conditions that can potentially reduce hepatic blood flow (e.g., severe congestive heart failure) may impair drug metabolism. Monitoring drug levels is advisable during continuous infusion.

Lidocaine toxicity from excessive plasma concentrations can result from poor cardiac output or from hepatic or renal failure. Elevated plasma levels beyond the therapeutic range can cause gastrointestinal symptoms (nausea and vomiting), central nervous system pathology (paresthesias, tremor, confusion, seizures), and, in rare instances, hemodynamic perturbations.

**Class II agents**

The class II drugs (esmolol, atenolol, metoprolol, and propranolol) block β-adrenergic receptors to variable extents (receptor selectivity and intrinsic sympathomimetic activity) depending on the specific agent. Anti-arrhythmic effects result from slowing conduction and decreasing automaticity, particularly in the sinoatrial and AV nodes. These drugs universally decrease sympathetic activity through β-receptor blockade.

**Esmolol**

Esmolol is a predominant β₁-selective (cardioselective) adrenergic receptor-blocking agent with a rapid onset and a very short duration of action. The drug’s primary electrophysiologic effect is inhibiting sinoatrial and AV conduction. Esmolol’s brief elimination half-life after IV injection (approximately 9 min) has made this drug desirable for use in perioperative and intensive care settings. Esmolol is commonly used to control heart rate and blood pressure and to manage a variety of tachyarrhythmias (supraventricular and ventricular) [76,77].

An IV loading dose of 100–500 μg/kg (over 1–2 min) can be administered. This is followed by a continuous infusion, starting at 50–100 μg/kg/min and titrated to effect. Because of esmolol’s short half-life, blood levels of the drug can be rapidly altered by increasing or decreasing the infusion rate, and the drug can be rapidly eliminated by discontinuing the infusion.

Most reported adverse effects related to esmolol therapy have been mild and transient. Reported cardiovascular side-effects include bradycardia, sinus pauses, AV block, hypotension, and negative inotropy. These are most likely to be seen during bolus therapy.

**Class III agents**

The class III drugs (amiodarone, sotalol, bretylium, ibutilide) block potassium channels and increase action potential duration and refractoriness in atrial and ventricular muscle and in Purkinje fibers. These agents should be avoided in patients with LQTS.

**Amiodarone**

Amiodarone has a wide spectrum of actions with multiple and complex electrophysiologic effects that encompass all four anti-arrhythmic drug classes. Class I actions include inhibition of fast sodium channels. Class II and IV effects result in depression of sinus node automaticity and function, and slowing of AV and His–Purkinje system conduction. As a class III agent, amiodarone delays repolarization and increases action potential duration, thereby prolonging refractoriness in all cardiac tissues and accessory connections if present. In addition to blocking potassium channels, amiodarone has vagolytic properties, weakly blocks calcium channels, and noncompetitively blocks α- and β-adrenergic receptors. The efficacy of this agent has been documented against many supraventricular (EAT, atrial flutter and fibrillation, reentrant arrhythmias involving accessory pathways, JET) and ventricular arrhythmias (VT and VF) [33,78–80]. The usefulness of this drug in the treatment of life-threatening tachyarrhythmias accounts for its expanding role in emergency cardiovascular management. In patients with an ICD, amiodarone may affect defibrillation thresholds.

Intravenous therapy requires a loading dose because of amiodarone’s rapid plasma disappearance during the distribution phase. The suggested dose in children is 5 mg/kg over 1 hour (may be given rapidly for life-threatening arrhythmias; max. dose 300 mg). The same dose is then infused over 12 hours and repeated if necessary. Amiodarone binds extensively to most tissues, which explains its extremely prolonged elimination and thus its unusually long half-life (average 58 days).

Amiodarone administration can result in sinus bradycardia and AV block. Hypotension is another potential complication of IV therapy and is probably due to calcium chelation. Electrocardiographic effects include PR, QRS, and QTc prolongation. There are significant drug interactions while using amiodarone that merit discussion. Co-administration with other anti-arrhythmic agents (digoxin, procanamide, flecainide, quinidine, phenytoin) can result in increased levels of these drugs. The concomitant use of the drug with β-blockers or calcium-channel antagonists should raise concerns about potential synergistic effects on conduction tissue. Several adverse effects have been reported with long-term oral therapy in children. These include skin discoloration, corneal microdeposits, alterations in hepatic and thyroid function, pulmonary fibrosis, and neurologic disturbances.

**Ibutilide**

Ibutilide is a class III agent approved in the adult population for acute intravenous therapy of atrial flutter and
fibrillation of recent onset (<90 days) [81–83]. Like other drugs that prolong ventricular repolarization, this agent can cause excessive QT prolongation and polymorphic VT, which necessitates careful patient selection and monitoring during drug administration. The clinical experience with ibutilide in pediatric patients is extremely limited [84].

Class IV agents
The class IV drugs, also known as calcium-channel blockers (verapamil, diltiazem, nifedipine), inhibit the slow inward calcium current.

Verapamil
The actions of this drug are mediated through prolongation of conduction time and refractory period in nodal tissue. Verapamil has been shown to be effective for managing SVT and certain types of VT [85–87].

Verapamil should not be used in young children (<1 year old) because of its potential to cause severe hemodynamic compromise (refractory hypotension, myocardial depression, asystole and cardiovascular collapse) [88,89]. The detrimental effects are related to calcium-channel blockade and uncoupling of excitation–contraction in myocardial cells. In older children (>1 year), verapamil is infused in a dose of 0.1 mg/kg. The concomitant use of verapamil and ß-blocking agents can result in serious cardiovascular side-effects and is therefore not recommended. In patients with WPW syndrome, verapamil can enhance the ventricular response rate of atrial fibrillation and lead to hemodynamic compromise.

Other agents
Atropine
Atropine sulfate, an antimuscarinic, parasympatholytic drug, accelerates sinus or atrial pacemakers and enhances AV conduction. Atropine is recommended for the treatment of symptomatic bradycardia caused by increased vagal activity or AV block, such as vagally mediated bradycardia during intubation. Atropine may be considered in the treatment of bradycardia associated with poor perfusion or hypotension; however, epinephrine is probably more effective for this condition. Efforts to ensure adequate oxygenation and ventilation and to exclude hypothermia should precede pharmacologic therapy of bradycardia.

The recommended dose is 0.02 mg/kg, with a minimum single dose of 0.1 mg and a maximum single dose of 0.5 mg in a child and 1.0 mg in an adolescent or young adult. The dose can be repeated 5 minutes later, to a maximum total dose of 1.0 mg in a child and 2.0 mg in an adolescent. In the absence of IV access, atropine (0.02 mg/kg) can be administered tracheally or intramuscularly, although with less reliable absorption than through the IV route. Small doses can be associated with transient heart rate slowing. Atropine can also rarely cause cardiac arrhythmias.

Digoxin
Digitalis glycosides have been used for many years in the management of certain arrhythmias. The electrophysiologic effects of digoxin are the result of its direct effects on cardiac tissues (through inhibition of the sarcolemmal sodium pump) and indirect effects via the autonomic (parasympathetic) nervous system. Digoxin increases the refractory period and decreases the conduction velocity of the specialized cardiac conduction system, slows the sinus rate (primarily by enhancing vagal discharge), and shortens the refractory period in atrial and ventricular muscle.

Digoxin can be effective in the treatment of a wide spectrum of supraventricular arrhythmias, such as SVT, atrial flutter, atrial fibrillation, and chaotic AT. In patients with WPW, digoxin is not recommended because it may alter the conduction properties of the accessory pathway and lead to malignant arrhythmias (VT and VF) during atrial flutter or fibrillation.

Digoxin can be administered orally or parenterally. Given that the onset of its effect may be delayed (up to 5 hours), this drug is less than ideal for treating acute symptomatic tachycardias. Despite this limitation, digitalis glycosides remain useful in controlling the ventricular response in atrial tachyarrhythmias, particularly during atrial flutter or fibrillation. A common loading algorithm uses a total oral digitalizing dose of 30–50 μg/kg. Half of this amount is given initially, followed by two doses at 6-hour intervals of 25% of the total dose. For IV use, the total digitalizing dose is reduced to 75% of the total oral dose given following a similar scheme. Maintenance doses of digoxin are 7–10 μg/kg/day. Digoxin binds tightly to peripheral tissue proteins, and drug excretion is via the kidneys. Dose adjustments are indicated in cases of renal impairment or congestive heart failure.

The co-administration of digoxin with other anti-arrhythmic agents (amiodarone, quinidine, verapamil) requires an adjustment (reduction) in the digoxin dose and monitoring of plasma levels. Toxic manifestations of digitalis therapy can be classified as cardiac and non-cardiac. Digoxin toxicity can cause virtually any type of cardiac rhythm disturbance. Non-cardiac manifestations of digitalis toxicity include gastrointestinal problems (nausea, vomiting, anorexia), neurologic symptoms (headache, lethargy, weakness, confusion, seizures), and visual disturbances. Although non-specific, non-cardiac symptoms are the earliest manifestations of digitalis toxicity.

Adenosine
Adenosine is a purine agonist, with effects mediated by the activation of the A1 adenosine receptor, leading to activation of adenylyl cyclase and intracellular cyclic adenosine monophosphate (cAMP) production. The electrophysiologic effects are secondary to an increase in potassium conductance and depression of the slow inward calcium current, resulting in transient sinus slowing or AV nodal block. This accounts for its therapeutic value in terminating arrhythmias that involve the AV node. Adenosine is the drug of choice for acute treatment of
SVT [47,48,90–93]. Adenosine can also aid the diagnosis of atrial tachyarrhythmias and may be useful in the differentiation of wide QRS tachycardias [91].

To terminate SVT, a bolus of IV adenosine is rapidly injected, preferably into a central vein, at initial doses of 100–150μg/kg, followed by a rapid normal saline flush. The dose can be doubled up to a maximum of 300μg/kg (or an adult dose of 6–12mg). The effects of the drug are seen within a period of 10–20 seconds. It is extremely useful to obtain an ECG recording during its administration because the response to adenosine may provide an insight into the mechanism of the tachycardia. Adenosine is rapidly metabolized by erythrocytes and endothelial cells, accounting for its extremely short half-life (<10 seconds).

Cardiac side-effects include sinus pauses, sinus bradycardia, AV block, atrial and ventricular arrhythmias, and reflex sinus tachycardia. These effects are generally transient and may only necessitate supportive care. However, the availability of temporary pacing and an external defibrillator may be prudent. Adenosine should be used with caution in patients who have undergone cardiac transplantation, because the electrophysiologic effects of this agent are increased in the denervated heart. Other unwanted effects are transient and generally well tolerated. These include flushing, shortness of breath, bronchospasm, and chest pressure. On very rare occasions, hypotension may occur.

Magnesium sulfate
Magnesium is a major intracellular cation, a co-factor in multiple enzymatic reactions, and an important regulator of numerous cardiovascular processes. Magnesium sulfate therapy is indicated as adjunct management for arrhythmias in patients with documented hypomagnesemia or torsades de pointes [77]. Magnesium deficiency is frequently seen in patients with other electrolyte abnormalities (hypokalemia and hypocalcemia). Rhythm disturbances associated with hypomagnesemia resemble those with hypokalemia or digitalis toxicity.

In torsades, IV infusion (over several minutes) of 25–50 mg/kg (up to 2 g) is recommended. Approximately 70% of plasma Mg²⁺ is ultrafiltered by the kidney, and the remainder is bound to protein. Side-effects associated with drug administration include flushing, diaphoresis, muscle weakness, and central nervous system depression. Magnesium levels well above the therapeutic range can lead to serious morbidity, such as cardiac conduction defects, respiratory depression, and circulatory collapse.

Dexmedetomidine
Dexmedetomidine is an α₂-adrenoceptor agonist with primarily sedative properties recently shown to have anti-arrhythmic effects as well. The exact mechanism of these effects is not well understood. It appears that central α₂-adrenoceptor-mediated enhancement of vagal neural activity plays a potential role [94]. A prospective observational study showed that during the perioperative period after cardiac surgery, receiving a continuous infusion of dexmedetomidine lowered patients’ risk of ventricular and supraventricular arrhythmias [95]. Other studies have also shown that the drug has a high success rate in the conversion of SVT [96,97].

**KEY POINTS: PHARMACOLOGIC THERAPY OF CARDIAC ARRHYTHMIAS**

- Anti-arrhythmic agents suppress abnormal rhythms or restore normal rhythm and conduction by their effects on blocking sodium, potassium, or calcium channels, or by altering adrenergic tone.
- Agents are usually categorized based on their mechanism of action into five main classes (Vaughan Williams classification).
- Some drugs have multiple sites of action, complicating the classification of these pharmacologic agents.
- Class III drugs should be avoided in patients with LQTS.
- The co-administration of certain anti-arrhythmic agents can result in increased levels of these drugs and potential synergistic effects on conduction.

**Pacemaker therapy in children**

**Pacemaker nomenclature**
Pacemaker nomenclature as established by the North American Society of Pacing and Electrophysiology and the British Pacing and Electrophysiology Group is detailed in Table 18.6 [98]. The generic pacemaker (NBG) code has five positions. The first position or letter of the code refers to the chamber(s) paced, the second to the chamber(s) sensed, the third to the pacemaker’s response to sensing, and the fourth to programmability and rate modulation. The fifth position is restricted to anti-tachycardia function and is used infrequently.

**Permanent cardiac pacing**
Advances in pacemaker technology, including enhancements in programmability and miniaturization of units, have resulted in the increasing use of these devices in infants and children [99]. Guidelines for device-based therapy of cardiac rhythm abnormalities were published by the American College of Cardiology, American Heart Association, and Heart Rhythm Society in 2008 and more recently by the European Society of Cardiology in collaboration with the European Heart Rhythm Association [100,101]. Box 18.2 lists indications in the guidelines document for children, adolescents, and patients with CHD for which there is general agreement that a pacemaker should be implanted (class I) and for which these devices are used frequently but diverging opinions exist regarding benefits (class II).
Table 18.6  Generic pacemaker code

<table>
<thead>
<tr>
<th>Position I</th>
<th>Position II</th>
<th>Position III</th>
<th>Position IV</th>
<th>Position V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chamber(s) paced</td>
<td>Chamber(s) sensed</td>
<td>Response to sensing</td>
<td>Programmability, rate modulation</td>
<td>Anti-tachyarrhythmic function(s)</td>
</tr>
<tr>
<td>O, none</td>
<td>O, none</td>
<td>O, none</td>
<td>O, none</td>
<td>O, none</td>
</tr>
<tr>
<td>A, atrium</td>
<td>A, atrium</td>
<td>I, inhibited</td>
<td>P, simple programmable</td>
<td>P, pacing</td>
</tr>
<tr>
<td>V, ventricle</td>
<td>V, ventricle</td>
<td>T, triggered</td>
<td>M, multiprogrammable</td>
<td>S, shock</td>
</tr>
<tr>
<td>O, none</td>
<td>O, none</td>
<td>O, none</td>
<td>O, none</td>
<td>O, none</td>
</tr>
</tbody>
</table>

Source: Bernstein et al. [98]. Reproduced with permission of Wiley.

Box 18.2: Recommendations for permanent pacing in children, adolescents, and patients with congenital heart disease

Class I (benefit >>> risk)
- Advanced second- or third-degree AV block associated with symptomatic bradycardia, ventricular dysfunction, or low cardiac output
- Sinus node dysfunction with correlated symptoms during age-inappropriate bradycardia. The definition of bradycardia varies with the patient’s age and expected heart rate
- Postoperative advanced second- or third-degree AV block that is not expected to resolve or that persists at least 7 days after cardiac surgery
- Congenital third-degree AV block with a wide QRS escape rhythm, complex ventricular ectopy, or ventricular dysfunction
- Congenital third-degree AV block in an infant with a ventricular rate < 55 bpm or with ventricular heart disease and a ventricular rate < 70 bpm

Class IIa (benefit >> risk)
- Prevention of recurrent episodes of IART in patients with CHD and sinus bradycardia; sinus node dysfunction may be intrinsic or secondary to anti-arrhythmic therapy
- Congenital third-degree AV block beyond the first year of life with an average heart rate < 50 bpm, abrupt pauses in ventricular rate that are two or three times the basic cycle length, or associated with symptoms due to chronotropic incompetence
- Sinus bradycardia, complex CHD, and either a resting heart rate < 40 bpm or pauses in ventricular rate > 3 seconds
- CHD and hemodynamic impairment due to sinus bradycardia or loss of AV synchrony
- Syncope that remains unexplained after careful evaluation of possible causes in patient with prior CHD surgery complicated by transient complete heart block and residual fascicular block

Class IIb (benefit > risk)
- Transient postoperative third-degree AV block that reverts to sinus rhythm with residual bifascicular block
- Congenital third-degree AV block in asymptomatic children or adolescents with an acceptable rate, narrow QRS complex, and normal ventricular function
- Asymptomatic sinus bradycardia after biventricular repair of CHD with a resting heart rate < 40 bpm or pauses in ventricular rate > 3 seconds

In general terms, potential indications for pacemaker implantation can be listed as follows:
- Symptomatic sinus bradycardia
- Recurrent bradycardia-tachycardia syndromes
- Congenital complete AV block
- Advanced second- or third-degree AV block

An important consideration in patients with CHD is correlation of symptoms with recommended criteria for pacemaker placement in view of the physiologic alterations associated with structural heart disease or postoperative intervention(s). The use of these devices in young patients and those with CHD presents unique challenges and considerations, some of which are highlighted in the sections that follow [102,103].

Implantation techniques
Permanent pacemaker implantation is performed via either the transvenous or the epicardial approach. These procedures usually take place under sterile conditions in the cardiac catheterization laboratory/electrophysiology suite, or in the operating room. In most infants and small children, the procedure requires a general anesthetic. In a select group of patients, mainly composed of older adolescents and adults, and depending on several factors, these types of procedures can be performed under local anesthesia with supplemental IV sedation.

The transvenous technique uses the subclavian vein as the most common site for access [104]. Under fluoroscopic guidance, pacing leads are advanced into the right atrium or ventricle, or both, and are fixed to the endocardium. After adequate lead sensing, capture thresholds, and impedances are documented, the leads are attached to a generator, which is typically positioned in the pectoral region. The following are considered contraindications to transvenous pacing: intracardiac communication with the potential for right-to-left shunting, prosthetic tricuspid valve, unsuitable anatomy for transvenous access to cardiac chambers, and small patient size (<10 kg). Advantages of the transvenous route include greater generator longevity (because of lower pacing thresholds) and lower incidences of lead fractures, particularly in active children [105]. The disadvantages are potential narrowing or thrombosis of venous pathways, lead dislocation, risk of systemic embolization in patients with an intracardiac shunt, and possible endocarditis.
For epicardial implantation, the leads are attached to the epicardial surface of the heart. After appropriate testing, the leads are tunneled to the generator pocket [106]. This approach requires a subcostal, subxiphoid, thoracotomy, or sternotomy incision. Advantages of epicardial implantation include ability for placement independent of cardiovascular pathology and avoidance of lead-related venous complications. Disadvantages include the invasiveness of the approach, higher incidence of lead failure, and early generator-battery depletion.

Hardware selection and programming of devices
A variety of hardware options are available for cardiac pacing in infants and children. The selection of a particular generator system, mode for pacing, and type of pacing leads is influenced by several factors, including patient size, indications for pacing, requirement for specific programmability options, underlying cardiac pathology, and anticipated need for generator longevity.

Both single- and dual-chamber units are commercially available for permanent pacing in pediatric patients. Dual-chamber devices provide the benefit of AV synchrony, thereby allowing for maintenance of the atrial contribution to ventricular filling, enhancing cardiac output, and lowering atrial pressures.

Cardiac resynchronization therapy requires placing two separate pacing leads in the right and left ventricles (biventricular pacing). The leads are implanted using a transvenous (left ventricular pacing accomplished via lead in the coronary sinus) or epicardial approach. The goal is to allow for electrical and mechanical synchrony in patients with intraventricular conduction delays in order to improve hemodynamics. This type of therapy has been used to a limited extent in older pediatric patients [107,108]. The most common indication is ventricular dyssynchrony related to a variety of cardiac diagnoses [109–114]. At the time of writing, no specific recommendations are available for the use of these devices in children or CHD patients.

Pacemaker malfunction
Pacemaker malfunction is most frequently caused by complications related to lead placement and integrity, failure to pace, failure to capture, under- or oversensing, phrenic nerve stimulation, and pacemaker-mediated tachycardia [115]. Pacemaker troubleshooting usually requires a 15-lead ECG, a rhythm strip, device interrogation to determine pacing and sensing thresholds, lead impedances, generator battery status and magnet rate, and a chest radiograph.

Children are considered to be at higher risk for lead failure and fracture than adults. These problems result in inappropriate pacemaker sensing or capture (underpacing or overpacing) and potential need for pacemaker revision. Adjusting pacemaker settings can temporarily remedy these issues.

Perioperative considerations
Patients with cardiac rhythm devices require special perioperative considerations (Box 18.3). The preoperative assessment of the patient with a pacemaker should include a complete history, with emphasis on indications for initial implantation, pacemaker dependency and underlying rhythm, coexistent cardiovascular pathology (structural or acquired), the functional status of the patient, and symptomatology. In addition, a focused physical examination should be performed that includes planned or existent pocket generator location [116]. Preoperative testing should be undertaken as indicated, including a chest radiograph that shows the number, position, and integrity of the pacing leads. If pacemaker details are needed but are not available, the device may have a code that can be read on a chest radiograph and used to identify the unit’s manufacturer/model.

### Box 18.3: Perioperative management of patients with cardiac rhythm devices

#### Preoperative preparation
- Determination of type of device and indication for pacing/ICD
- Assessment of underlying rhythm and pacemaker dependency
- Evaluation of device function (pacemaker check, ECG, CXR)
- Consideration of reprogramming to asynchronous mode
- Deactivation of rate adaptive functions
- Disabling of anti-tachycardia function/defibrillation mode as appropriate

#### Intraoperative management
- Intraoperative monitoring (continuous ECG, monitoring of effective cardiac output; e.g., pulse oximetry, cuff blood pressure, arterial line)
- Availability of backup temporary pacing and cardioversion-defibrillation equipment
- Immediate availability of drugs (isoproterenol, emergency agents)
- Avoidance of electromagnetic interference (bipolar electrocautery preferable; place grounding pad so current passes far away from pacemaker and leads)
- Availability of magnet (not to replace preoperative evaluation or to be used instead of reprogramming device)

#### Postoperative considerations
- Continuous ECG monitoring, pulse oximetry, cuff pressure, or arterial line
- Immediately availability at all times of backup pacing and cardioversion-defibrillation equipment
- Interrogation of device, reprogramming as needed
- Reactivation of special modes (anti-tachycardia, defibrillation mode for ICDs, and others)

CXR chest radiograph, ECG electrocardiogram, ICD implantable cardioverter-defibrillator.

Device interrogation should be part of a complete preoperative evaluation in all patients with implanted pacemakers who are scheduled for surgical intervention (cardiac or non-cardiac) [116–118]. Consultation with
a pediatric cardiologist/electrophysiologist to obtain details of unit type, settings, date of and indications for implantation, and underlying rhythm is highly recommended. The patient’s pacemaker card, if available, may also provide relevant information. Results of a recent 15-lead ECG should also be reviewed. Reprogramming may be necessary before the planned procedure to avoid potential problems with pacemaker malfunction related to electromagnetic interference (EMI), such as that produced by electrocautery or radiofrequency ablation. If there is a significant risk of EMI and the patient is pacemaker-dependent, it is recommended that the pacemaker be reprogrammed to asynchronous mode [91]. The introduction of bipolar leads, improved filters, and circuit shields has made modern devices less susceptible to EMI. The rate-responsive mode, if turned on, should be deactivated, as should anti-tachycardia modes. Several case reports suggest that incomplete perioperative evaluations can lead to adverse outcomes [119,120]. Pacemaker dysfunction has been found in up to 12% of patients undergoing preoperative interrogation before undergoing non-cardiac surgery, highlighting the importance of preoperative assessment [121].

Regarding intraoperative management, it should be considered that unipolar electrocautery can interfere with pacemaker function, so bipolar electrocautery is preferred. The diathermy grounding pad should have good skin contact and be placed as far away from the device as possible. In addition to routine perioperative monitoring, which includes ECG and pulse oximetry, other modalities that confirm pulse generation during pacing, such as manual pulse palpation, auscultation (via precordial or esophageal stethoscope), and invasive arterial blood pressure monitoring, should be considered. Chronotropic agents and alternate pacing modalities (transcutaneous, transvenous, transesophageal, epicardial) should be readily available in the event of pacemaker malfunction and inadequate underlying heart rate. If defibrillation is required, the current should not be applied to or passed directly through the pulse generator, because this may damage the device circuitry.

A magnet should always be accessible to allow for transient asynchronous pacing if required. Most generators respond to magnet application by pacing asynchronously at a fixed rate (AOO, VOO, or DOO). It should be emphasized, however, that the settings of the asynchronous programmed stimuli for magnet mode varies among pacemaker units. Furthermore, at generator end of life, the pacing rate on magnet application may differ (i.e., be slower) from the pre-specified magnet rate or cause pacing to stop altogether. In some cases, the application of a magnet over a programmable pacemaker during EMI (i.e., cautery) may result in generator reprogramming [122]. Therefore, a magnet should never be considered a substitute for preoperative pacemaker interrogation or programming, nor should it be used routinely over a pacemaker generator during surgery or to offset potential EMI. After the procedure is completed, the device should be retested and programmed to baseline settings as appropriate.

**Temporary cardiac pacing**

The transvenous and epicardial routes are commonly used for temporary pacing, although the transthoracic (transcutaneous) and transesophageal approaches are also suitable in some cases. Indications for temporary cardiac pacing are not as clearly defined as those for permanent pacing [123]. Recent literature suggests that there is no need for routine placement of temporary epicardial pacing wires after congenital heart surgery [124,125]. However, in patients who undergo surgical interventions such as the Fontan operation or procedures performed under circulatory arrest, or who have intraoperative arrhythmias, postoperative temporary pacing has been shown to improve hemodynamics; thus, such patients would probably benefit from the placement of pacing wires at the time of surgery [126].

Temporary pacing is achieved by placing special wires in the atrial and/or ventricular epimyocardium toward the completion of the surgical procedure and before sternal closure [6,123,127]. As previously stated, atrial wires usually exit to the right of the sternum and ventricular wires to the left. Wires should be clearly labeled to prevent confusion if there is no institutional convention. Pacing in the atrium and ventricle is termed AV sequential pacing. During pacing, the electrical impulse originates at the pulse generator – in this case, a temporary pacing box – and then flows through the wires. Unipolar and bipolar epicardial pacing leads are available. A unipolar lead is a single wire conductor (electrode at tip), whereas a bipolar lead has two conductors within a single wire. During unipolar pacing, the electrical current flows from the electrode in contact with the heart (cathode, negatively charged) to a wire placed in the subcutaneous tissue that serves as the electrode (anode, positively charged) receiving the electrical impulse after the cardiac tissue is depolarized. In bipolar pacing, the electrical current flows through the electrode at the distal tip of the lead wire (negative cathode), and after stimulation of the heart, the signal returns to the more proximal electrode (positive anode). Bipolar systems tend to require less energy for pacing, and there is less electrical interference during sensing. The negative cathode (the epicardial wire in unipolar systems; the distal epicardial wire in bipolar units) should be clearly labeled; this is the wire that should be connected to the negative terminal of the pulse generator.

Several programmable settings are available in the external temporary pulse generator (single- or dual-chamber device). Depending on the unit, these include pacing rate, atrial or ventricular output amplitude (milliamperes, mA), atrial or ventricular sensitivity (mV) or asynchronous mode, A-V interval (milliseconds), post-ventricular atrial refractory period, and upper rate tracking. The most important parameters to be adjusted are rate, chamber output, and pacing mode. Adjustments in optimal sensing
and pacing parameters are guided by testing of thresholds. The following is a brief overview of pacemaker settings and how these parameters are adjusted:

- **Rate.** This should be set at a physiological rate for age, or to provide adequate cardiac output during the postoperative state. If overdrive suppression of an arrhythmia is needed, the rate is usually set 10 to 20% higher than the arrhythmia rate.

- **Sensitivity.** The sensing threshold represents the minimum electrical activity that the pacemaker is able to sense. The lower the sensitivity setting, the less electrical activity is required by the pacemaker to sense, or a greater sensitivity. To determine sensitivity, the pacemaker rate is set lower than the underlying rate in a synchronous pacing mode (AAI, VVI, or DDD). The sensitivity number is then increased (lowering sensitivity) until the sense indicator on the generator stops flashing (this implies that the mode is being changed to asynchronous pacing; see below). The sensitivity setting (number) on the generator is then decreased (increasing sensitivity) until the sense indicator flashes in each cardiac depolarization. This setting represents the sensing threshold. Sensitivity is then set at half of the sensing threshold. Typically, if no underlying rhythm is present, sensitivity is set at 2 mV. It should be emphasized that setting the sensitivity to a higher number renders the pacemaker insensitive, meaning that the mode is changed from demand to asynchronous or fixed-rate pacing. Conversely, using a very low sensitivity setting could make the pacemaker oversensitive, potentially risking pacemaker inhibition (failure to pace) by inappropriate sensing of events that are interpreted as electrical cardiac activity.

- **Capture thresholds.** This parameter indicates the minimum amount of energy (current intensity) required to stimulate the action potential in the myocardium. To determine this setting, the pacemaker rate should be set above the underlying rate so that the pacemaker is consistently pacing the chamber being tested. The output is then slowly decreased until there is no longer capture of this chamber. The minimum output at which capture is still present is the capture threshold. Output should be set at twice the capture threshold to increase the margin of safety. Setting the output too high results in atrial and ventricular activation, it should be recognized that optimal hemodynamics may not be achievable. This pacing modality has not been found to be effective in the treatment of asystole in children.

- **AV delay.** This represents the PR interval. In most cases, this parameter is set automatically according to rate or to between 100 and 150 msec.

Temporary pacing may be necessary for maintaining adequate cardiac output in patients with bradycardias, abnormal AV conduction, AV asynchrony, and inadequate heart rates for physiologic state [128]. It may also be helpful in individuals at risk of high-degree AV block and can be used to suppress, overdrive, or terminate tachyarrhythmias. As previously discussed, atrial recordings obtained through temporary pacing wires can also provide diagnostic information in certain types of rhythm disorder. In the care of patients who depend on temporary pacing for maintenance of adequate hemodynamics, it is extremely important to be attentive to pacemaker settings and capture thresholds, which should be interrogated on a daily basis [127]. Testing should include determining underlying rhythm, whether ongoing pacing is needed, and the battery status of the temporary pacemaker. It is preferred to lower the pacing rate until the endogenous rhythm comes through to determine the underlying rhythm, rather than decreasing the output until capture is lost, pausing or turning off the pacemaker, or detaching the leads. Alternate means of pacing should be available in the event of lead or pacemaker failure or malfunction. A second pulse generator and battery should be available at all times. Temporary pacing can be discontinued when the indication for pacing resolves or when transition to a permanent pacing system is required.

### External cardiac (transcutaneous) pacing

In the mid-1980s, a transcutaneous external cardiac pacing system was patented and introduced by Dr. Paul Zoll [129]. Over the ensuing years, there was renewed interest in the field and further enhancements in the technology. Most devices currently available for transcutaneous pacing combine defibrillation/cardioversion capabilities and external pacing features. In children, emergency transthoracic pacing can be considered as a temporizing measure for symptomatic bradycardia (secondary to abnormal sinus node function or to complete AV block) [130]. Because transcutaneous pacing results in simultaneous atrial and ventricular activation, it should be recognized that optimal hemodynamics may not be achievable. This pacing modality has not been found to be effective in the treatment of asystole in children.

Transcutaneous pacing electrodes (pads) are selected according to patient size (smaller ones for children <15 kg). When gel pads are applied prophylactically, an ECG tracing obtained directly from the pads confirms adequate skin contact and proper cable attachment to the unit in case pacing is required. Device settings for pacing typically include heart rate and current output (mA). Most available models provide the option for demand or fixed pacing mode. After the desired heart rate and pacing modality are selected, the output is increased until capture is achieved. In emergency situations, pacing should be initiated at or near the maximum current output, and once capture is documented, pacing can be gradually decreased to 5–10 mA above the capture threshold. Sedation may be necessary to improve pacing tolerance in the awake patient because this mode of pacing can be associated with discomfort (burning skin sensation, contraction of skeletal muscles). Prolonged periods of transcutaneous pacing can result in serious burns or skin trauma in infants and young children.
In addition to monitoring for pacemaker capture by an ECG, ongoing clinical assessment of pulse, blood pressure, and adequacy of cardiac output should be undertaken.

**Transesophageal overdrive pacing**

An esophageal catheter can be used for atrial sensing, which provides diagnostic information and enables discrimination between supraventricular tachyarrhythmias. Using the esophageal route also allows for overdrive pacing of a variety of supraventricular rhythm disorders (e.g., atrial flutter, SVT). For this purpose, an electrode catheter is inserted into the esophagus and advanced to a location that corresponds roughly to the region behind the atrial mass, and an AEG is obtained to better position the catheter. Local anesthesia of the nasopharynx or oropharynx and/or sedation is generally necessary for introducing the catheter and preventing discomfort during atrial pacing. Standard cardiorespiratory monitoring should be performed throughout the procedure, and airway support should be provided as necessary. Emergency drugs and cardioversion/defibrillation equipment should be readily available.

**Implantable cardioverter-defibrillators**

The primary purpose of an ICD is to prevent sudden death in patients at high risk. Although sudden cardiac death is uncommon in pediatric patients, those with certain conditions are at sufficiently high risk to make them suitable candidates for ICD implantation. These conditions include hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, LQTS, Brugada syndrome, and a history of near sudden death events [131,132]. Placement of an ICD may also be warranted in pediatric patients with operated CHD or a history of malignant arrhythmias.

Device implantation involves lead and generator placement. An issue of concern is the high rate of lead failure, which is reportedly 21% in children and young adults [133]. A subcutaneous ICD that does not require lead placement is available in Europe and is currently undergoing investigation in the US [134]. At present, experience in the pediatric age group with ICD devices in general is limited and is reported mostly in retrospective fashion [135–139]. Prospective trials are required to establish guidelines for use, address safety concerns, and evaluate long-term issues specific to children.

Anesthetic considerations in patients with ICDs relate primarily to potential surgical EMI (from electrocautery) and the need for an available external cardioverting/defibrillating device. Perioperative consultation with a specialist is therefore essential. In most cases, the device must be deactivated or adjusted before surgery. Application of a magnet temporarily deactivates most but not all devices; thus, it is not a substitute for reprogramming and should only be considered in emergencies. Careful evaluation and device programming are advisable at the conclusion of the surgical intervention to ensure patient safety.

**KEY POINTS: PACEMAKER THERAPY IN CHILDREN**

- Indications for permanent pacing in children in most cases relate to symptomatic sinus bradycardia, recurrent bradycardia-tachycardia syndromes, congenital complete AV block, and advanced second- or third-degree AV block.

- Patients with implanted cardiac rhythm devices require special perioperative considerations during anesthetic care.

- Temporary pacing wires are placed toward the end of surgery in patients who may require or potentially benefit from pacing perioperatively; the wires also serve to assist in arrhythmia recognition/treatment.

- The most important settings for temporary cardiac pacing are heart rate, chamber output, and pacing mode.

- Temporary pacemaker settings and thresholds should be interrogated on a daily basis in the postoperative period.

- A magnet should never be used as a replacement for preoperative pacemaker interrogation or reprogramming, nor should it be used intraoperatively to offset potential EMI.

**Summary**

A significant portion of cardiac anesthesia practice involves caring for patients affected by cardiac rhythm disturbances or who may develop perioperative or periprocedural arrhythmias. It is well recognized that patients with CHD, both children and adults, represent a subgroup who are particularly vulnerable to the negative hemodynamic consequences associated with alterations of cardiac rhythm. Knowledge of cardiovascular diseases affecting cardiac rhythm, arrhythmia mechanisms, diagnosis, drug therapy, and alternative therapeutic options is essential for optimal patient care and limiting related morbidity.

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http://www.wiley.com/go/andropoulos/congenitalheart

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CHAPTER 19
Airway and Respiratory Management

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**Introduction**

Airway and respiratory management of infants and children with congenital heart disease (CHD) during diagnostic and surgical procedures presents unique challenges to the anesthesiologist owing to a range of congenital airway abnormalities, cardiopulmonary interactions, and adverse effects of surgery and cardiopulmonary bypass (CPB). Few other clinical situations will tax the skills of an anesthesiologist more than the management of a child with CHD and a difficult airway. Children with cardiovascular disease may be intolerant of the myocardial depressant effects of many anesthetics, limiting the options available in managing their airway during induction of anesthesia. Children with cyanotic CHD experience rapid oxygen desaturation during periods of apnea associated with tracheal intubation. Developing a plan that allows safe airway and respiratory management without hemodynamic compromise requires preparation, skill, and familiarity with a range of techniques of tracheal intubation.

**Choosing the appropriate endotracheal tube**

Cuffed vs. uncuffed
The narrowest portion of the of a child’s larynx is at the level of the cricoid cartilage, as opposed to adult patients whose limiting airway diameter is at the level of the vocal cords (rima glottidis) [1]. Uncuffed endotracheal tubes (ETTs) are commonly used in children because a seal is created between the tracheal mucosa and the tube at the level of the cricoid cartilage. A tight-fitting ETT (e.g., no gas leak up to 30–35 cmH\(_2\)O) may cause ischemic injury to the tracheal mucosa and submucosa at the level of the cricoid cartilage. This is a substantial risk in children undergoing cardiac surgery, in whom the ETT may remain in place for extended periods of time following surgery. Mild ischemia and subsequent swelling may be manifest as post-extubation stridor, whereas subglottic stenosis may result from more severe injury [2]. On the other hand, placement of an ETT with a gas leak at low...
inflating pressures (e.g., <15 cm H₂O) results in excessive leak around the ETT. This is particularly important for thoracic or cardiovascular surgery because lung compliance may be reduced as a result of surgical traction or pulmonary edema, resulting in the delivery of greater inflating pressures to provide physiologic tidal volumes. With a loose-fitting ETT in place, the volume of gas leak around the ETT increases as the peak inflating pressure is increased, while alveolar ventilation decreases. Gas leakage representing more than 50% of tidal volume has been demonstrated in the setting of decreasing lung compliance [3]. Associated decreases in minute ventilation may lead to dangerous elevations in PaCO₂ and difficulty in reinflating atelectatic lung tissue following CPB. Table 19.1 presents a scheme for selection of ETT size in infants and children.

In addition to the risk of inadequate alveolar ventilation, there are other hazards associated with placement of a loose-fitting ETT. Lung function measurements are commonly used to guide mechanical ventilation in the postoperative period. A variable leak around the ETT results in inaccurate measurements of exhaled tidal volumes, lung compliance, and airway resistance. Eliminating or minimizing the gas leak around the ETT will decrease the environmental pollution from either inhaled anesthetic agents or nitric oxide [4]. Lastly, an adequate seal around the ETT may decrease the risk of pulmonary aspiration should gastric contents be regurgitated following tracheal intubation.

Traditional teaching has recommended the use of uncuffed ETTs in children under the age of 8 years. However, there is limited scientific evidence to support this practice. Cuffed ETTs have been used in more than 15,000 children, none of whom developed clinically significant airway complications [5], and the use of cuffed ETTs for short cases in the operating room reduces the need for repeated laryngoscopy, allows use of lower fresh gas flows, and limits environmental contamination with anesthetic gases [4]. There is no difference in the incidence of airway complications among pediatric patients intubated with cuffed vs. uncuffed ETTs when studied in pediatric intensive care units or operating rooms [6, 7]. However, the need to exchange ETTs is significantly greater when using uncuffed ETTs. Alterations in mucosal edema and lung compliance from the effects of CPB or altering pulmonary blood flow (PBF) may increase the leak around the ETT in children after heart surgery, and a cuffed ETT may be inflated to compensate for such changes. In a retrospective review of 809 children < 2 years old undergoing cardiac surgery over a 4-year period, the incidence of subglottic stenosis (17/809 or 1.08%) was not affected by the common use of cuffed ETT in the series. The most important risk factors were younger age and prolonged (>96 hours) postoperative ventilation [8]. Lastly, there is some evidence suggesting that children with CHD require larger ETTs [9].

A disadvantage of using cuffed ETTs is that their outer diameter is approximately 0.3–0.5 mm larger than uncuffed ETTs with the same inner diameter. As a result, a tube with an inner diameter one size (i.e. 0.5 mm) smaller is recommended when a cuffed ETT is placed. This results in greater resistance to gas flow and an increased risk of occlusion of the ETT with blood and tracheal secretions. While a reduction of the tracheal tube diameter by only 0.5 mm might not be expected to effect a clinical change, gas flow resistance increases exponentially at smaller tube diameters. While a reduction in tracheal tube size from 8.0 mm to 7.5 mm internal diameter (ID) increases airway resistance by 29%, a change in tube size from 4.0 to 3.5 mm ID results in an increase of 71%, and a change from a 3.5 mm to a 3.0 mm ID tube increases resistance by 85%. The increase in resistance is even more profound if turbulent airflow occurs in smaller tracheal tubes.

The microcuff ETT (Kimberly-Clark, Roswell, GA, USA) has been developed for pediatric patients that provides a true high-volume, low-pressure cuff, eliminates the Murphy eye in order to optimize cuff position at the tip of the ETT, and an ultrathin cuff that provides an outer diameter to inner diameter ratio similar to uncuffed ETTs. Two studies including 575 patients aged 0–5 years have found a low incidence of post-extubation stridor, and a tracheal tube exchange rate of <3% [9, 10]. The routine use of cuffed ETTs is now recommended by many experts [11,12].

### Table 19.1 Endotracheal tube sizes used in pediatric patients

<table>
<thead>
<tr>
<th>Age</th>
<th>Size (mm ID)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm</td>
<td>2.5</td>
</tr>
<tr>
<td>&lt; 1,000 g</td>
<td>2.5</td>
</tr>
<tr>
<td>1,000 g – 2,500 g</td>
<td>3.0</td>
</tr>
<tr>
<td>Term neonate – 6 months</td>
<td>3.5</td>
</tr>
<tr>
<td>6 months – 1 year</td>
<td>4.0</td>
</tr>
<tr>
<td>1 – 2 years</td>
<td>4.0 – 5.0</td>
</tr>
<tr>
<td>Beyond 2 years</td>
<td>(Age (years) + 16)/4</td>
</tr>
</tbody>
</table>

ID, inner diameter. A cuffed endotracheal tube generally has outer diameter 0.5 mm greater than an uncuffed tube.

### KEY POINTS: ADVANTAGES OF CUFFED ENDO TRACHEAL TUBES

- There is consistent tidal volume delivery with changing pulmonary compliance.
- They allow improved measurement of pulmonary mechanics.
- Environmental pollution is reduced.
- There is a decreased risk of pulmonary aspiration.
- There is no difference in the incidence of airway complications compared with uncuffed endotracheal tubes.

### Orotracheal vs. nasotracheal intubation

While orotracheal intubation is performed more commonly than nasotracheal intubation for routine surgery in children, there may be advantages to the use of nasal ETTs in children undergoing cardiac surgery. Transesophageal echocardiography (TEE), which is performed in many...
centers, may cause compression or dislodgement of an orotracheal tube in the oropharynx. However, Stevenson found a low incidence of airway complications during pediatric TEE among children who were orally intubated [13]. Of the 1650 patients he studied, three (0.2%) developed a right mainsteam advancement of the ETT, and eight (0.5%) were inadvertently extubated. Nasal ETTs are more readily secured to the face, and movement of the ETT is less likely during manipulation of the TEE probe. At Texas Children’s Hospital, over 6,000 TEE studies have been performed in children who were nasally intubated, with two inadvertent extubations in the past 17 years. There is a greater risk of damage to nasal alae and, in older children, of sinusitis from long-term nasotracheal intubation [14–16]. The risk of bleeding from adenoidal trauma is especially problematic in the fully anticoagulated patient. This risk is minimized by the routine use of topical vasoconstrictor drugs (e.g., oxymetazoline) and adequate lubrication of the ETT. Excessive pressure should not be used during advancement of the tube through the nose and nasopharynx. Prior to advancing the ETT into the nasopharynx, a soft, lubricated suction catheter can be passed through the ETT through the nasopharynx into the oral cavity. This will act as a guide permitting easier passage of the nasal ETT [17]. Because ETTs can be placed more easily and rapidly via the oral route, oral intubation is preferred for rapid sequence intubation or when intubating cyanotic infants. Once adequate ventilation and oxygenation have been provided and the stomach is suctioned, the ETT may be exchanged for a nasal tube under direct visualization. Because it is important to properly determine the appropriate size of the ETT, some practitioners intubate most children undergoing cardiac surgery orally, perform a leak test and alter the size of the tube, or use a cuffed ETT if necessary via the nasal route. In general, the nasal passages of children will accommodate the same size ETT as would be used for oral intubation.

The difficult airway

The incidence of congenital airway anomalies has been demonstrated to be greater among children with CHD than in the general population. Akpek et al. reported a retrospective review of 1,278 pediatric cardiac surgery patients, and observed a 1.25% incidence of difficult tracheal intubation [18]. Of the 16 difficult airways, all were two-ventricle patients, and eight had known genetic or dysmorphic syndrome. Micrognathia, macroglossia, restricted neck movement, and tracheal deviation were causes of difficult intubation. Another retrospective review by Heinrich et al. of over 11,000 pediatric patients in a multi-specialty operating room practice reported that pediatric cardiac surgery patients (944 of the total) had an incidence of difficult laryngoscopy of 3.6%, significantly higher than the overall population of 1.35%, and exceeding any other subspecialty surgery group, including oral-maxillofacial surgery [19]. In their cardiac patients, incidence was higher in patients less than 1 year of age (5.6% vs. 1.7% > 1 year, P < 0.001). Velocardiofacial syndrome and CHARGE associations were the most frequently associated syndromes; interestingly, trisomy 21 was not associated with difficult laryngoscopy [20]. Syndromes associated with both airway anomalies and CHDs are frequent, and patients with syndromes such as the CHARGE association (Coloboma of the iris, Heart defects, Atresia choanae, Retardation of mental and somatic growth, Genitourinary anomalies, Ear malformations and deafness) and velocardiofacial syndrome (diGeorge syndrome; partial chromosome 22q11.2 deletion, CATCH-22 syndrome) must have a complete airway examination. A thorough history should be taken of all patients receiving sedation or anesthesia with attention to the recent presence of an upper respiratory tract infection, snoring or noisy breathing during sleep, inspiratory stridor, and previous problems associated with tracheal intubation or following extubation. In older, cooperative patients, the airway should be examined as with adult patients, including mouth opening, dentition, mandibular size (hyomental distance), and neck mobility. Studies in adults have shown that examination of the airway can help to predict difficulty of intubation and mask ventilation [21]. No such studies have been performed in infants and children, and it is not known whether assessing mouth opening using a tongue depressor in a non-verbal child is predictive of difficulty with intubation. Assessment of an infant’s airway should include an assessment of neck mobility and the appearance of the mandibular size when viewed in profile. Children with micro- or retrognathia are more likely to manifest difficult mask ventilation and/or difficult intubation.

Intubation of the patient with a difficult airway

A modification of the American Society of Anesthesiologists (ASA) algorithm for the management of the patient with a difficult airway can be applied to children [22] (Figure 19.1). Specialized airway equipment should be prepared, checked, and available in the operating room. Box 19.1 lists recommendations for equipping a difficult airway cart. In addition to equipment, additional personnel skilled in airway management should be immediately available for assistance.

When the difficult airway is recognized prior to the induction of anesthesia, control of the airway can be performed with the patient awake, following sedation, or after the induction of anesthesia with inhalation agents. Awake, non-sedated, direct laryngoscopy can be accomplished in neonates but may be difficult, traumatic, and have significant adverse hemodynamic consequences. Placement of a laryngeal mask airway (LMA) after application of topical anesthesia to the airway in an awake infant has been described as an alternative to awake direct laryngoscopy [23]. Fiberoptic-guided intubation of the older, cooperative patient using topical anesthesia and intravenous sedation is a safe and effective alternative.
Inhalation induction of anesthesia using sevoflurane with maintenance of spontaneous ventilation is commonly performed in infants and children with a difficult airway. Intravenous access is established prior to mask induction. If the patient develops airway obstruction during the induction of anesthesia, immediate attempts are made to relieve the obstruction by jaw thrust, head extension, use of continuous positive airway pressure (CPAP), and insertion of an oropharyngeal or nasopharyngeal airway. If mask ventilation is inadequate and not improved with these maneuvers, insertion of an LMA should be attempted. If positive pressure ventilation (PPV) can be delivered via the LMA, the LMA can be used as a guide for insertion of an ETT or can be exchanged for an ETT with the use of a fiberoptic bronchoscope (FOB). If an LMA fails to provide a patent airway, preparations should
be made for an emergency cricothyrotomy (see later). If mask ventilation is possible with either a facemask or an LMA, neuromuscular relaxation can be used in order to optimize laryngoscopy.

If mask ventilation is possible, but tracheal intubation is not readily achieved, one should optimize head and neck positioning and consider use of an alternate laryngoscope blade to better visualize the larynx. In recent years, videolaryngoscopes in pediatric sizes have become available and may be considered (see later). Repeated attempts at direct laryngoscopy may lead to swelling and/or bleeding in the airway and the inability to perform adequate mask ventilation. After three to four failed attempts at direct laryngoscopy, use of an LMA should be considered. For the majority of pediatric patients, insertion of an LMA provides a patent airway and a method of delivering PPV, and facilitates fiberoptic intubation.

**Fiberoptic-guided tracheal intubation**
The development of FOBs with small diameters has facilitated the use of fiberoptic-guided intubation in infants and young children. A pediatric FOB with a 2.2 mm outer diameter that will fit through a 3.0 mm (ID) ETT tube is available (Olympus LF-P, Olympus America Inc., Melville, NY, USA). A FOB with an outer diameter of 2.4 mm that passes through a 3.0 mm (ID) ETT is also manufactured (Pentax Intubation FI-7P, Pentax Precision Instrument Corporation, Orangeburg, NY, USA). Neither of these FOBs has a suction channel. Currently, the smallest FOB that has a suction channel is 2.8 mm in diameter (available from Karl Storz, Tuttlingen, Germany and Olympus America Inc., Melville, NY, USA). Fiberoptic-guided tracheal intubation can be performed via the nose, mouth, or LMA, under sedation and topical anesthesia or under general anesthesia. The nasal route may be preferred because it tends to maintain the scope in the midline, facilitating visualization of the larynx. Repeated practice in children with normal airways is recommended in order to acquire and maintain the skills essential to be proficient with the use of this equipment.

Fiberoptic-guided tracheal intubation can also be performed through an LMA. Once the LMA is appropriately positioned, the FOB is passed through the opening of the LMA into the trachea. An ETT is passed into the trachea over the FOB, which is then used to confirm appropriate positioning. When a standard ETT is used, only a short length of the ETT remains outside the LMA, making maintenance of ETT position and removal of the LMA difficult. A variety of techniques have been described to facilitate safe removal of the LMA while maintaining the ETT in place. First, a specially designed, long ETT can be passed through the FOB. Secondly, a tracheal tube exchange catheter (Cook Critical Care, Inc., Bloomington, IN, USA) can be passed through the ETT into the trachea, after which both the ETT and LMA are removed. An ETT is passed over the exchange catheter into the trachea. Thirdly, the ETT can be made temporarily longer by wedging a half size smaller ETT into the proximal end, or by cutting the 15 mm adapter and using it to connect two ETTs of the same size together. After placement of the combined ETTs through the LMA, the LMA and proximal ETT are removed and the 15 mm adapter is replaced. Lastly, long forceps typically used for rigid bronchoscopy can be used to hold the ETT while the LMA is removed. An alternative to fiberoptic intubation through the LMA is “blind” passage of the ETT through the LMA into the trachea. An intubating LMA has been developed for this purpose and is now available in smaller sizes. In younger children, the epiglottis frequently folds inside the LMA [24]. While this may not cause airway obstruction, traumatic injury to the epiglottis may occur from blind passage of an ETT.

Several other methods for controlling the airway of patients with a difficult airway have been described. These include the use of a lighted stylet, combitube, retrograde transtracheal intubation, blind nasal intubation, use of other specialized laryngoscopes with or without video capability, and digital (tactile) techniques [25, 26]. The reader is referred to a textbook of general pediatric anesthesiology for more detailed descriptions of these alternative techniques for intubation.

**Videolaryngoscopic intubation**
The videolaryngoscope has made a significant contribution to management of difficult tracheal intubation in adult patients and is now prominently featured in the ASA difficult airway management practice guidelines as the first option for alternative approaches to intubation on the non-emergency pathway [22]. However, despite miniaturization of a number of these devices for pediatric patients, facility with these instruments by pediatric anesthesiologists has not been as great, and both laryngoscopic view and ability to insert the ETT into the trachea may be more difficult in small infants and children with micgnathia, for example, than in adult patients with more typical causes of difficult intubation such as obesity. [27]. Available videolaryngoscopes for pediatrics include the Glidescope® (Verathon Medical, Bothell WA, USA), and the C-MAC® videolaryngoscope (Karl Storz Company, Tutingen, Germany). Before utilizing these techniques in a pediatric cardiac patient with a difficult airway, the anesthesiologist should become thoroughly familiar with their use and limitations in other settings [27].

**Emergency cricothyrotomy**
In the rare instance in which mask ventilation and placement of an LMA do not provide adequate oxygenation and ventilation and tracheal intubation cannot be performed, percutaneous cricothyrotomy may be life-saving. Percutaneous tracheotomy kits are available (Cook Critical Care, Inc.) that are designed to facilitate pediatric tracheotomy tube placement through the cricoid membrane using the Seldinger technique [28].
The overall effect of the lateral decubitus position on V/Q mismatch, however, is unique in infants. In adults with unilateral lung disease, oxygenation is optimal when the patient is placed in the lateral decubitus position with the healthy lung dependent (“down”) and the diseased lung non-dependent (“up”) [35]. Presumably, this is related...
to an increase in blood flow to the dependent, healthy lung and a decrease in blood flow to the non-dependent, diseased lung, due to the hydrostatic pressure (or gravitational) gradient between the two lungs. This phenomenon optimizes V/Q matching in the adult patient undergoing thoracic surgery in the lateral decubitus position.

In infants with unilateral lung disease, however, oxygenation is improved with the healthy lung “up” [36]. Several factors account for this discrepancy between adults and infants. Infants have a soft, easily compressible rib cage that cannot fully support the underlying lung. Therefore, FRC is closer to residual volume, making airway closure likely to occur in the dependent lung even during tidal breathing [37]. When the adult is placed in the lateral decubitus position, the dependent diaphragm has a mechanical advantage, because it is “loaded” from abdominal pressure. This pressure is reduced in infants, thereby reducing the functional advantage of the dependent diaphragm. The infant’s small size also results in a reduced hydrostatic pressure gradient between the non-dependent and dependent lungs. Consequently, the favorable increase in perfusion to the dependent, ventilated lung is reduced in infants. This may be especially true for infants with systemic-to-pulmonary artery shunts, e.g., modified Blalock–Taussig (BT), PDA, or multiple aortopulmonary collateral arteries, in whom systemic pressure may be maintained in the pulmonary arterial circulation.

Finally, all infants have increased oxygen consumption, which predisposes them to hypoxemia. Infants normally consume 6–8 mL O₂/kg/min compared with adults’ 2–3 mL/kg/min [38]. The FRC of the lung serves as an oxygen reservoir when ventilation ceases. An infant will more rapidly consume oxygen from the diminished oxygen reservoir that is produced during surgery in the lateral decubitus position. Infants with cyanotic CHD are at increased risk of life-threatening oxygen desaturation during thoracic surgery.

**Key Points: Ventilation/Perfusion in the Lateral Decubitus Position**

- In adults with unilateral lung disease, oxygenation is optimal when the patient is placed in the lateral decubitus position with the healthy lung dependent (“down”) and the diseased lung non-dependent (“up”).
- In infants with unilateral lung disease, however, oxygenation is improved with the healthy lung “up”.

**Single-lung ventilation**

Before 1995, nearly all thoracic surgery in children was performed by thoracotomy; however, today, many thoracic procedures can be performed using video-assisted thoracoscopic surgery (VATS). Reported advantages of thoracoscopy include smaller chest incisions, reduced postoperative pain, and more rapid postoperative recovery compared with thoracotomy [39–41]. VATS is now being utilized for PDA occlusion in many centers. Open thoracotomy is generally performed for more complex procedures, including repair of coarctation of the aorta and pulmonary artery unifocalization. Single-lung ventilation (SLV) is desirable during VATS as well as open thoracotomy because lung deflation improves visualization of thoracic contents and may reduce lung injury caused by the use of retractors. There are several different techniques that can be used for SLV in children.

**Single-lumen ETT**

The simplest means of providing SLV is to intentionally intubate the ipsilateral mainstem bronchus with a conventional single-lumen ETT. When the left bronchus is to be intubated, the bevel of the ETT is rotated 180° and the head is turned to the right [42]. The ETT is advanced into the bronchus until breath sounds on the operative side disappear. A fiberoptic bronchoscope may be passed through or alongside the ETT to confirm or guide placement. When a cuffed ETT is used, the distance from the tip of the tube to the proximal cuff must be shorter than the length of the bronchus so that the cuff is entirely in the bronchus [43]. This technique is simple and requires no special equipment other than a fiberoptic bronchoscope, and may be the preferred technique of SLV in emergency situations, such as airway hemorrhage or contralateral tension pneumothorax.

Problems can occur when using a single-lumen ETT for SLV. If a smaller, uncuffed ETT is used, it may be difficult to provide an adequate seal of the intended bronchus. This may prevent the operative lung from collapsing adequately, or fail to protect the healthy, ventilated lung from contamination by purulent or bloody material from the contralateral lung. It is not possible to suction the operative lung using this technique. Hypoxemia may occur due to obstruction of the upper lobe bronchus, especially when the short right mainstem bronchus is intubated. Microcuff ETTs have a thinner-walled cuff positioned at the tip of the ETT and therefore may be advantageous for use in SLV.

Variations of this technique have been described, including intubation of both bronchi independently with small ETTs [44–47]. One mainstem bronchus is initially intubated with an ETT, after which another ETT is advanced over a fiberoptic bronchoscope into the opposite bronchus.

**Balloon-tipped bronchial blockers**

A Fogarty embolectomy catheter or an end-hole, balloon wedge catheter may be used for bronchial blockade to provide SLV [48–51]. Placement of a Fogarty catheter is facilitated by bending the tip of its stylette toward the bronchus on the operative side. A fiberoptic bronchoscope may be used to position the catheter and confirm appropriate placement. When an end-hole catheter is placed outside the ETT, the bronchus on the operative
side is initially intubated with an ETT. A guidewire is then advanced into that bronchus through the ETT. The ETT is removed and the blocker is advanced over the guidewire into the bronchus. An ETT is then reinserted into the trachea alongside the blocker catheter. The catheter balloon is positioned in the proximal mainstem bronchus under fiberoptic visual guidance. With an inflated blocker balloon, the airway is completely sealed, providing more predictable lung collapse and better operating conditions than with an ETT in the bronchus.

A potential problem with this technique is dislodgment of the blocker balloon into the trachea. The inflated balloon will then block ventilation to both lungs and/or prevent collapse of the operated lung. The balloons of most catheters currently used for bronchial blockade have low-volume, high-pressure properties and over-distension can damage or even rupture the airway [52]. Guyton et al., however, reported that bronchial blocker cuffs produced lower “cuff to tracheal” pressures than double-lumen tubes [53]. When closed tip bronchial blockers are used, the operative lung cannot be suctioned and CPAP cannot be provided to the operative lung if needed.

Adapters are available that facilitate ventilation during placement of a bronchial blocker through an indwelling ETT [54,55]. A 5 Fr endobronchial blocker that is suitable for use in children with a multiport adapter and fiberoptic bronchoscope is commercially available (Arndt Bronchial Blocker, Cook Critical Care, Inc.) [56]. The risk of hypoxemia during blocker placement is diminished, and repositioning of the blocker may be performed with fiberoptic guidance during surgery. Even with use of a 2.2-mm-diameter FOB, however, the indwelling ETT must be at least 4.5 mm ID to allow passage of the catheter and FOB. The use of this technique, therefore, is generally limited to children over the age of 18 months.

**Univent™ tube**

The Univent™ tube (LMA North America, San Diego, CA, USA) is a conventional ETT with a second lumen containing a small tube that can be advanced into a bronchus [57–59]. A balloon located at the distal end of this small tube serves as a blocker. Univent™ tubes require a fiberoptic bronchoscope for successful placement. Univent tubes are available in sizes as small as a 3.5 and 4.5 mm ID for use in children over 6 years of age [60]. Because the blocker tube is firmly attached to the main ETT, displacement of the Univent blocker balloon is less likely than when other blocker techniques are used. The blocker tube has a small lumen which allows egress of gas and can be used to insufflate oxygen or suction the operated lung, but this feature is only present in size 6.0 and larger Univent tubes.

A disadvantage of the Univent tube is the large amount of cross-sectional area occupied by the blocker channel, especially in the smaller size tubes which have a disproportionately high resistance to gas flow [61]. The Univent tube’s blocker balloon has low-volume, high-pressure characteristics so that mucosal injury can occur during normal inflation [62,63].

**Double-lumen tubes**

All double-lumen tubes (DLTs) are essentially two tubes of unequal length molded together. The shorter tube ends in the trachea and the longer tube in the bronchus. DLTs for older children and adults have cuffs located on the tracheal and bronchial lumens. The tracheal cuff, when inflated, allows PPV. The inflated bronchial cuff allows ventilation to be diverted to either or both lungs, and protects each lung from contamination from the contralateral side.

The smallest cuffed DLT is 26 Fr (Rusch, Duluth, GA, USA) and may be used in children as young as 8 years old. DLTs are also available in sizes 28 and 32 Fr (Mallinckrodt Medical, Inc., St. Louis, MO, USA), suitable for children of 10 years and older.

In children, DLTs are inserted using the same technique as in adults [64]. The tip of the tube is inserted just past the vocal cords and the stylette is withdrawn. The DLT is rotated 90° to the appropriate side and then advanced into the bronchus. In the adult population, the depth of insertion is directly related to the height of the patient [65]. No equivalent measurements are yet available in children. If fiberoptic bronchoscopy is used to confirm tube placement, a scope with a small diameter and sufficient length must be available [66].

A DLT offers the advantage of ease of insertion as well as the ability to suction and oxygenate the operative lung with CPAP. Left DLTs are preferred to right DLTs because of the shorter length of the right main bronchus [67]. Right DLTs are more difficult to position accurately because of the greater risk of right upper lobe obstruction.

Double-lumen tubes are safe and relatively easy to use. There are very few reports of airway damage from DLTs in adults, and none in children. Their high-volume, low-pressure cuffs should not damage the airway if they are not overinflated with air or distended with nitrous oxide while in place. Compared with bronchial blockers, a higher incidence of minor airway trauma has been reported with the use of DLTs in adults [68].

Guidelines for selecting appropriate tubes (or catheters) for SLV in children are shown in Table 19.2. There is significant variability in overall size and airway dimensions in children, particularly in teenagers. The recommendations shown in Table 19.2 are based on average values for airway dimensions. Larger DLTs may be safely used in large teenagers.

**Ventilatory management during thoracic surgery**

During two-lung ventilation, tidal volumes of 8–10 mL/kg are typically used at a respiratory rate that provides normocapnia. When one lung is ventilated, the delivered tidal volume should be reduced to ≤ 6–8 mL/kg and the respiratory rate increased by 20% in order to avoid excess inspiratory pressure and volume to the ventilated lung. Pulse oximetry and capnography are useful to reflect trends in the changes in oxygenation and ventilation, but monitoring of arterial blood gas tensions is important.
to accurately determine PaO₂ and PaCO₂ during SLV in infants and children with congenital cardiac disease.

Hypoxemia is commonly encountered during thoracic surgical procedures, especially in children with CHD and pre-existing hypoxemia, pulmonary hypertension, or impaired myocardial function. Hypoxemia develops from one or more possible mechanisms. The conducting passages of the operative lung are intentionally obstructed during SLV and/or from surgical retraction and compression of the operative lung. Secretions in the airways, and surgical and hydrostatic compression may also compromise gas flow through the conducting passages of the dependent lung. The reduction in ventilation to the operative lung produces regional hypoxemia, inducing HPV, which will reduce V/Q mismatch. However, HPV may be impaired and will not improve V/Q matching in children with CHD. In a dog model, it has been shown that HPV is impaired by elevated pulmonary arterial pressure and by low mixed venous oxygen tension, both of which are commonly encountered among children with CHD [69,70]. Lastly, retraction of the operative lung may compress the mediastinum, impairing cardiac filling and reducing cardiac output, which decreases mixed venous oxygen concentration, thereby worsening hypoxemia from either intracardiac or intrapulmonary shunting.

Severe hypoxemia should be treated immediately by increasing the FiO₂ to 1.0 and by confirming patency of the ETT. A suction catheter should be passed through the ETT to clear secretions and/or blood from the lumen. Irrigation with sterile saline may be performed. If the ETT remains occluded, a FOB may be used to determine the site of obstruction and to re-establish patency of the ETT. The surgeon should be informed, and compression of the lung and/or mediastinum should be minimized. Administration of intravenous fluids may improve cardiac output and improve V/Q matching by increasing perfusion pressure to the lungs. Application of CPAP with 100% O₂ to the non-dependent lung will reduce shunt through this lung and improve oxygenation during SLV. If hypoxemia persists despite these maneuvers, the operative lung should be re-inflated with 100% oxygen. Although nitric oxide might be expected to increase PBF to the ventilated lung and improve oxygenation, two studies in adults failed to show benefit from nitric oxide during SLV [71,72].

Some degree of hypoxemia is common during SLV. In a study of 52 children without CHD undergoing SLV during VATS, a decrease in SpO₂ occurred in 40% of patients in whom a bronchial blocker was used [73]. The bronchial blockers used did not have lumens for administration of CPAP/O₂. Forty percent of patients in this study also had PaCO₂ values >50 mmHg, although the clinical significance of hypercarbia was not documented. In another study of 12 pediatric patients in whom VATS was performed for closure of PDA, CO₂ insufflation and hypercarbia (PaCO₂ of 50–70 mmHg) was not associated with circulatory impairment [74]. In fact, the authors reported that hypercarbia was associated with increased cardiac output and central venous O₂ and arterial O₂ tension in these patients. The specific mechanism of these effects of hypercarbia, e.g. changes in pulmonary to systemic blood flow (Qp:Qs), were not described.

### KEY POINTS: TREATMENT OF SIGNIFICANT HYPOXEMIA THAT DEVELOPS DURING SLV

- Increase FiO₂ to 1.0.
- Inform the surgeon.
- Suction the ETT, use sterile saline if there are thick secretions.
- Change anesthetic technique to minimize HPV
- Pass the FOB through the ETT to determine patency.
- Apply CPAP to the non-dependent lung.
- If there is no improvement, discontinue SLV and ventilate the operative lung.

### Changes in lung function in children with CHD

Ventilation may be impaired in children with increased PBF due to left-to-right shunts. Both decreased lung compliance and increased airway resistance have been demonstrated in these children. Two studies in infants and young children with CHD found strong correlation between echocardiographic evidence of pulmonary artery engorgement and decreased lung compliance [75,76]. A study of neonatal patients undergoing thoracotomy for BT shunts or repair of coarctation of the aorta [77] determined that lung compliance decreased and airway resistance was significantly increased after surgery. However, the return to baseline pulmonary function was prolonged after BT shunt placement when compared with coarction repair, suggesting that increases in PBF worsen pulmonary

<table>
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<tr>
<th>Age (years)</th>
<th>ETT (ID mm)a</th>
<th>BBb(Fr)</th>
<th>Univent™c (ID mm)</th>
<th>DLT (Fr)d</th>
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<td>6.0 cuffed</td>
<td>6</td>
<td>3.5</td>
<td>26</td>
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<tr>
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<td>6.5 cuffed</td>
<td>6</td>
<td>4.5</td>
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<tr>
<td>16–18</td>
<td>7.0–8.0 cuffed</td>
<td>7</td>
<td>7.0</td>
<td>35</td>
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*aSheridan Tracheal Tubes, Kendall Healthcare, Mansfield, MA, USA.*
*bArrow International Corp., Redding, PA, USA.*
*cLMA North America, San Diego, CA, USA.*
*d26 Fr (Rusch, Duluth, GA, USA); 28–35 Fr (Mallinckrodt Medical, Inc., St. Louis, MO, USA).*

d, internal diameter in mm, Fr, French size, DLT, double-lumen tube.
mechanics [77]. Some infants develop substantial increases in total lung resistance following heart surgery, the severity of which can be predictive of postoperative respiratory failure [78]. Acute increases in pulmonary artery pressure also produce significant changes in lung mechanics. Airway resistance increases 43% and compliance decreases 11% during periods of acute pulmonary hypertension [79]. In this study, lung biopsy specimens from patients with the greatest increase in pulmonary artery pressure had increased bronchial smooth muscle mass, suggesting that the same local mediators that affect increases in pulmonary arterial pressure produce bronchospasm. Changes in lung mechanics correlate better with the magnitude of pulmonary vascular engorgement than with pulmonary artery hypertension. During cardiac catheterization, the degree of increased PBF is proportionate to increases in respiratory resistance among infants who are mechanically ventilated [80]. Infants with CHD and pulmonary overcirculation have reduced dynamic compliance and increased respiratory resistance that improve following surgery [81].

Extrinsic compression of larger airways by the heart and vascular structures can also affect lung function in children with CHD. Both left and right mainstem bronchial compression have been described from enlarged pulmonary arteries. An enlarged left atrium can compress the left mainstem bronchus, and bronchial compression can occur from extrinsic compression by a right ventricle-to-pulmonary artery conduit [82].

**Changes in lung function from CPB**

Pulmonary dysfunction is common after cardiac surgery [83]. Children with increased PBF may develop up to a three-fold increase in lung water in the immediate postoperative period, the degree of which appears to be related to the presence of pulmonary hypertension [84,85]. In addition, both quantitative and qualitative differences in surfactant have been described in children after CPB [86]. Others have found the most common adverse pulmonary effect is the development of atelectasis, reported to be as high as 82% among children undergoing CPB [87]. Both non-cardiogenic pulmonary edema and acute bronchospasm have also been reported following CPB in children and adults, [88,89], although the incidence of these complications in children is unknown. Some authors found correlation between the duration of CPB and the severity of lung injury, while others found only minor changes in pulmonary mechanics related to CPB [87,90–92]. These differences may be related to improvements in CPB management over the past decade. In a study of over 100 infants undergoing heart surgery, there was no correlation among the duration of CPB, the duration of aortic cross-clamp, the use of deep hypothermic circulatory arrest, and pulmonary outcomes [93].

**Cardiopulmonary interactions**

Positive intrathoracic pressure typically has adverse hemodynamic effects on the right ventricle and variable hemodynamic effects on the left ventricle in patients with normal cardiac anatomy and function. Intrathoracic pressure is transmitted to the thin-walled, compressible superior and inferior venae cavae, reducing venous blood return to the right atrium and leading to a decrease in right ventricular filling [94]. In addition, right ventricular output will decrease if pulmonary vascular resistance (PVR) increases from hyperinflation of the lungs. With acute rises in PVR, the right ventricle may become dilated, resulting in decreased left ventricular filling as the intraventricular septum is displaced to the left [95].

Pulmonary vascular resistance is affected by mechanical factors, chemical factors, and local humoral factors. PVR is optimal when the resting lung volume is at FRC and becomes elevated when lung volumes are above or below FRC. As lung volume decreases below FRC, extra-alveolar (large) blood vessels are compressed. In addition, atelectasis develops when lung volume decreases, leading to HPV with associated elevation in PVR. When lung volumes exceed FRC, alveolar distension causes compression of smaller arterioles and capillaries, also resulting in an increase in PVR [96] (Figure 19.2). Both oxygen tension and pH have significant effects on PVR [97], with alveolar hypoxemia and acidemia causing an increase in PVR, and alkalemia reducing PVR. Local pH has the greatest affect on pulmonary vascular tone, and PVR is reduced by producing either respiratory or metabolic alkalemia. Finally, lung expansion from PPV causes a local release of prostaglandins, leading to pulmonary vasodilation. This may explain the decrease in PVR associated with the onset of hyperventilation that occurs before CO2 is reduced [97].

Changes in pleural pressure also affect left ventricular function. Ventricular output is affected by changes in afterload of the ventricle from transmitted intrathoracic pressure to the ventricular wall. The left ventricle lies...
within the thoracic cavity, whereas most of the systemic arterial tree lies outside the thoracic cavity. Therefore, changes in pleural pressure affect the left ventricle and not the systemic vasculature. Afterload is affected by the ventricular transmural pressure, i.e., the intracavitary pressure minus the pleural pressure. During spontaneous ventilation, negative intrapleural pressure is transmitted to the ventricular wall. During systole, the ventricle must overcome systemic vascular resistance (SVR) and pleural pressure, and therefore afterload is increased when negative pleural pressure develops as occurs during spontaneous ventilation. With PPV, SVR is unchanged, but afterload to the ventricle is reduced because positive intrapleural pressure will reduce ventricular transmural pressure [98–100] (Figure 19.3).

**Mechanical ventilation for children with CHD**

Changes in pleural pressure during inspiration have different hemodynamic effects on patients with cardiac and/or pulmonary disease. In healthy individuals, spontaneous inspiration augments venous return and increases right ventricular output, while increasing left ventricular afterload and decreasing left ventricular output. The net effect on total cardiac output is minor, and the conversion to PPV will have minimal effects on cardiac output. However, in hypovolemic patients, total cardiac output decreases from PPV because the decrease in right ventricular preload produces the predominant hemodynamic effect.

In patients with right heart failure, mechanical ventilation parameters should be selected that will minimize intrathoracic pressure, maintain lung volume at FRC, avoid hypoxemia, and optimize pH in order to minimize PVR. Intrathoracic pressure should be minimized by avoiding excess positive end-expiratory pressure (PEEP) and excessive tidal volumes. However, inadequate PEEP will cause lung volumes to decrease below FRC, thereby increasing PVR. Pressure–volume loops can be used to optimize pulmonary mechanics (Figure 19.4). Hyperventilation is the traditional maneuver performed to reduce PVR because the associated hypocarbia produces alkalosis. However, both metabolic and respiratory alkalosis reduce PVR [97,101]. Local tissue pH is the most significant factor affecting tone in pulmonary vessels. Because hyperventilation requires an increase in minute ventilation, greater intrathoracic pressure must be used, which may reduce right ventricular preload. Creating a metabolic alkalosis through the administration of sodium bicarbonate will produce the same beneficial effect on reducing PVR without interfering with right ventricular filling. Acute increases in pulmonary pressure often produced profound hypotension, because left ventricular filling is significantly impaired from both a reduction in preload (right heart output) and a shift of the intraventricular septum as the right heart dilates. Diastolic hypotension

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**Figure 19.3** The effect of positive pressure ventilation on systemic ventricular transmural pressure. $P_{Ao}$, aortic pressure; $P_{pl}$, pleural pressure.

**Figure 19.4** Relationship of lung volume to pulmonary vascular resistance. FRC, functional residual capacity.
reduces coronary perfusion to a stressed myocardium, which may rapidly result in cardiovascular collapse (see Chapter 28 for further detailed discussion of pulmonary hypertension).

Positive pressure ventilation may improve cardiac output among patients with left ventricular systolic failure [102,103]. As the left ventricle fails and begins to dilate, left atrial pressure is increased, leading to pulmonary venous congestion and decreased lung compliance. The work of breathing is increased and greater negative pressure is generated during spontaneous ventilation, which, in turn, increases left ventricular afterload. PPV will decrease the work of breathing and thereby decrease oxygen consumption. In addition, positive intrathoracic pressure will reduce ventricular afterload, enhancing cardiac output. However, patients with diastolic ventricular dysfunction will have small stroke volumes as a stiff, hypertrophied myocardium does not adequately relax. The reduction in preload from PPV produces the predominating effect on cardiac output. Studies on patients with tetralogy of Fallot, who commonly have right ventricular diastolic dysfunction, show that cardiac output increases with negative pressure ventilation [104]. Patients with non-pulsatile PBF (e.g., following the bidirectional cavopulmonary shunt and Fontan procedures) show the most dramatic interactions between alterations in intrathoracic pressure, PBF, and cardiac output. Because pulsatile flow in the pulmonary arteries is absent, positive intrathoracic pressure interferes with PBF. Likewise, elevations in PVR will reduce PBF. Reductions of PBF impair ventricular filling and reduce cardiac output. The goals of lowering PaCO$_2$ in order to reduce PVR while diminishing intrathoracic pressure are diametrically opposed. A pattern of ventilation providing large tidal volumes (e.g., 10–15 mL/kg) with lower respiratory rates is believed to optimize carbon dioxide elimination and PBF. PEEP is generally avoided in order to diminish intrathoracic pressure. However, atelectasis and lung volumes below FRC will increase PVR and these problems can be minimized through the use of PEEP.

As opposed to the larger tidal volumes, modern lung-protective ventilation strategies in both adults and children with acute respiratory distress syndrome and other causes of acute respiratory failure are now generally utilized for longer-term ICU ventilation, and indeed have been shown to improve pulmonary outcomes in neonatal and pediatric patients. Limiting peak pressures to less than 30 cmH$_2$O and tidal volumes to 6–8 mL/kg are now generally accepted ventilation strategies in ICU patients with acute respiratory failure [105–108].

Negative pressure ventilation produces a significant improvement in stroke volume and PBF over that of conventional PPV [109]. High-frequency jet ventilation effectively reduces PaCO$_2$ at a lower mean airway pressure than conventional mechanical ventilation and has been shown to improve cardiac output when compared with conventional ventilation in postoperative Fontan patients [110].

In patients with lung diseases associated with collapsed or fluid-filled alveoli (atelectasis, pulmonary edema, pneumonia, acute respiratory distress syndrome), gas exchange will improve when FRC is re-established through the use of PEEP. In this setting, the application of positive pressure and PEEP will have variable cardiovascular effects depending on lung compliance. Even high levels of PEEP have limited effect on cardiac output when lung compliance is reduced, because the higher airway pressures are not transmitted to the heart and pulmonary vasculature [111]. Some congenital heart defects such as tetralogy of Fallot with absent pulmonary valve are associated with small and large airway compression from engorged pulmonary arteries. These patients develop airway collapse during exhalation and typically manifest hyperinflation of some lung segments and/or atelectasis in other areas [112]. Such children benefit from a ventilatory strategy that increases exhalation time, i.e., a slower ventilatory rate allowing prolonged exhalation. The optimal level of PEEP can be determined through the use of pressure–volume and flow–volume loops. (Figure 19.4).

Airway pressure release ventilation (APRV) is a mode of mechanical ventilation utilizing CPAP with an intermittent release phase. APRV applies CPAP (P high) for a prolonged time (T high) to maintain adequate lung volume and alveolar recruitment, with a time-cycled release phase to a lower set of pressure (P low) for a short period of time (T low) or (relax time) where most of ventilation and CO$_2$ removal occurs. APRV has been described in a growing number of patients with acute lung injury (ALI), because lung volume is maintained with less volutrauma throughout the ventilatory cycle compared with intermittent mandatory ventilation. Patients may breathe spontaneously during APRV; in the absence of spontaneous ventilation, APRV is equivalent to “inverse ratio” pressure control ventilation [113]. Human and animal studies have shown improved oxygenation, better V/Q matching and decreased dead space with APRV compared with conventional mechanical ventilation in the presence of ALI, possibly related to the beneficial effects of spontaneous breathing [114]. Improved cardiac function has been described with APRV in patients with ALI. Improved hemodynamics in adults with ALI on APRV vs. pressure-controlled ventilation include higher cardiac index, oxygen delivery, mixed venous oxygen saturation, and urine output (mL/kg/hour) and significantly lower vasopressor and inotrope usage, lactate concentration, and CVP [115]. Studies of APRV in children also show favorable results. An early study of APRV in children with mild-to-moderate lung disease (without CHD) showed comparable levels of ventilation and oxygenation at significantly lower inspiratory peak and plateau pressures compared with intermittent mandatory ventilation [116]. A more recent study showed that APRV, at comparable mean airway pressure, improves lung perfusion compared with pressure control ventilation in children after tetralogy of Fallot repair and cavopulmonary shunt operations [117].
KEY POINTS: MECHANICAL VENTILATION FOR CHILDREN WITH CHD

- Spontaneous ventilation (negative intrathoracic pressure) will increase cardiac output in:
  - patients with right ventricular diastolic dysfunction, such as tetralogy of Fallot;
  - patients with non-pulsatile pulmonary blood flow, such as bidirectional Glenn or Fontan.
- Positive pressure ventilation and PEEP will increase cardiac output in patients with left ventricular dysfunction and volume overload.

Lung management during CPB

Studies performed in animal models and adult patients have compared the use of continuous mechanical ventilation, intermittent sigh breaths, and CPAP during CPB. Most studies show improvement in postoperative gas exchange with CPAP; however, this difference appears to be short-lived [118,119]. No such studies have been performed in children. Because closing capacity is higher in infancy, maintaining airway patency through the application of CPAP would theoretically be beneficial. Lung inflation from CPAP, however, may interfere with adequate surgical access to the heart and complete lung collapse is usually required. An FiO\textsubscript{2} of 0.21 vs. 1.0 has the theoretical benefit of diminishing absorption atelectasis during CPB, although this has not been studied in children either. Before weaning from CPB and after confirmation of the absence of air in the left atrium and ventricle, vital capacity breaths should be administered in order to re-establish patency of collapsed airways, re-inflate atelectatic areas of the lung, and mobilize secretions into the larger airways. The tracheal tube should be suctioned prior to weaning from CPB to assure patency of the tracheal tube and large airways, but care must be taken in order to avoid tracheal mucosal injury that may produce hemorrhage in a fully anticoagulated patient. Inhaled β\textsubscript{2} agonists are commonly administered before weaning from CPB in order to decrease airway reactivity; however, the efficacy of this practice has not been proven.

Volume control vs. pressure control ventilation

Volume-limited, time-cycled ventilation delivers a relatively constant tidal volume despite changes in the patient’s total pulmonary compliance. During volume-controlled ventilation, the peak inspiratory pressure varies and is dependent on the set tidal volume, PEEP, gas flow rate, gas flow resistance, and respiratory system compliance. The presence of high inflation pressures signals decreased pulmonary compliance or conductance (e.g., offset of neuromuscular blockade, bronchospasm) or obstruction of the breathing circuit (e.g., occluded ETT). Disadvantages of volume-limited ventilation include the potential to produce very high inflating pressures and increase the risk of barotrauma. With proper monitoring of inspiratory pressure, including the use of appropriate limits and alarms, changes in the patient’s pulmonary mechanics can be observed and the risk of barotrauma minimized. Because of technical difficulties in accurately delivering very small tidal volumes (e.g., < 100 mL), volume-limited ventilators have been primarily used in patients over 10 kg body weight. More recently, however, ventilators have been introduced that may be used in a volume-limited mode for smaller patients [121,122].

In the neonate and infant, ventilators that are pressure-limited and time-cycled are commonly used. These ventilators offer the advantages of avoiding excessive inflating pressures and barotrauma. However, a decrease in the compliance or conductance of the patient’s respiratory system, ventilator circuit, or tracheal tube will cause a reduction in delivered tidal volume. Conversely, an increase in compliance will result in an increased tidal volume and the risk of “volutrauma.” Pressure-limited or pressure control ventilation is frequently applied to infants and children receiving mechanical ventilatory support in which severe pulmonary pathology dictates the need for rapid respiratory rates or high inflating pressures. Advantages of this mode of ventilation include limiting the peak inflating pressure delivered by the ventilator, thereby limiting the transalveolar pressure and ventilator-induced lung injury [123]. The decelerating flow used to produce pressure control ventilation is thought to improve the distribution of gas flow to the lungs [124]. When compared with volume control ventilation, there is a more rapid improvement in lung compliance and oxygenation with pressure control ventilation [125]. Some anesthesia ventilators may not deliver small tidal volumes accurately because of the proportionately large compression volume loss in the ventilator and circuit [126]. Therefore, setting an anesthesia ventilator in pressure control mode will deliver more consistent ventilation to infants when the anesthesia machine cannot compensate for compression volume loss in the entire circuit [126].

Monitoring ventilation

Ventilation is the tidal exchange of gas between lungs and the atmosphere, and is measured by the concentration of CO\textsubscript{2} in arterial blood (PaCO\textsubscript{2}). In the operating room, the most common non-invasive method of measuring CO\textsubscript{2} is capnography, which closely reflects changes in PaCO\textsubscript{2} among patients without lung or heart disease. Capnography is less accurate in infants when there is a leak around the ET and when CO\textsubscript{2} is measured at the Y piece due to fresh gas washout of the small volume of CO\textsubscript{2} sampled [127]. Infants with right-to-left intracardiac shunting will have an increased end-tidal to arterial CO\textsubscript{2} gap due to bypassing of the lungs by the shunted blood. The relationship is variable, but in general increasing...
cyanosis and decreasing PBF will increase the end-tidal to arterial difference [128]. Acutely increasing PBF (i.e., by placement of a systemic-to-pulmonary artery shunt) will decrease the end-tidal to arterial CO$_2$ gap. Finally, low PBF states, i.e., partial CPB, cardiac arrest, or low cardiac output syndrome, will decrease end-tidal CO$_2$ independent of ventilation, and an increasing end-tidal CO$_2$ heralds increased PBF, i.e., separating from bypass, return of spontaneous circulation, or improved cardiac output [129].

Another measurement of alveolar ventilation is the measurement of exhaled tidal volumes. Exhaled tidal volume is usually measured by a spirometer located at the end of the expiratory limb. This measurement tends to be an overestimate because it reflects the patient’s exhaled tidal volume and the compression volume in the breathing circuit. As a result, the measured exhaled tidal volume may be inaccurate in infants. If there is a leak around the ETT, the spirometer will underestimate the exhaled gas volume. Without reliable end-tidal CO$_2$ monitoring or exhaled tidal volume measurements, the pediatric cardiovascular anesthesiologist must rely on chest expansion and peak inspiratory measurement (PIP) to make ventilator adjustments. Because adult anesthesia ventilators have large compression volumes, only profound changes in lung compliance are reflected in changes in PIP. For these reasons, blood gases should be measured frequently in order to assure adequate ventilation and to recognize changes in acid–base status. Newer monitoring systems allow for measurement of flow and pressure at the ETT, assisting the anesthesiologist in determining optimal ventilation in patients with poorly compliant lungs. Newer anesthesia machines that compensate for breathing circuit compliance, such as the Aisys anesthesia ventilator systems (GE Healthcare, Madison, WI, USA) and the Apollo anesthesia ventilator (Dräger Medical, Telford, PA, USA), provide accurate measures of delivered tidal volume [130].

**Anesthesia ventilators**

Efforts to improve the design of anesthesia ventilators have been directed towards improving the accuracy of volume ventilation so that the patient reliably receives a tidal volume that is as close as possible to the set tidal volume. Newer generation anesthesia machine ventilators that compensate for breathing circuit compliance and for fresh gas flow are able to deliver small tidal volumes accurately to the airway under conditions of normal and low lung compliance during volume-controlled ventilation. Anesthesiologists should be aware that long, compliant circuits reduce the efficiency of ventilator performance, and changing the circuit compliance by extending a collapsible circuit will reduce tidal volume delivery [126]. When providing ventilation for an infant with poor lung compliance, using a fixed length circuit with smaller hoses that are less compliant will optimize the anesthesia ventilator performance. Also, dead space ventilation can be reduced by eliminating the Y-piece and using a low dead space heat and moisture exchanger that contains a gas sampling port. In very small infants (e.g., < 2.5 kg) and patients with very poor chest compliance, ICU ventilators may be needed.

**Specialized problems**

**Hypoxic gas mixture and inspired CO$_2$**

Infants and children with single-ventricle physiology and excess PBF (e.g., those with hypoplastic left heart syndrome) may benefit from a ventilatory strategy designed to increase PVR and diminish PBF. Hypoxic gas mixtures (i.e., FiO$_2$ < 0.21) or inhaled CO$_2$ have been used to accomplish this. Among neonatal patients with single-ventricle physiology, 3% inhaled CO$_2$ improves cerebral oxygen saturation, mean arterial pressure and oxygen delivery when compared with 17% inspired oxygen [131,132]. In addition, the ventilator setup for delivering hypoxic gas mixtures invariably involves blending in nitrogen, and thus there is the potential for unintended administration of a very hypoxic gas mixture [133]. Hypoxic gas mixture delivery has largely been abandoned for these reasons, and many preoperative hypoplastic left heart syndrome patients are currently not intubated, instead being left to regulate their Qp:Qs by employing room air spontaneous ventilation, with early surgery planned before PBF becomes excessive.

**Nitric oxide**

Inhaled nitric oxide (iNO), an endothelium-derived smooth muscle relaxant, is a selective pulmonary vasodilator and can acutely decrease pulmonary artery pressure and PVR without affecting cardiac index or SVR. iNO is approved for the treatment of hypoxemic respiratory failure associated with pulmonary hypertension in term/near-term neonates [134,135]. Because congenital heart lesions with left-to-right shunts may be complicated by pulmonary arterial smooth muscle hyperplasia and hypertrophy associated with pulmonary hypertension, iNO is also used in these patients [136,137]. In particular, iNO may be specific treatment for patients following CPB, which causes pulmonary vascular endothelial injury and resultant decreased nitric oxide synthesis [138]. In one study, infants with pulmonary hypertension after cardiac surgery had a decrease in pulmonary artery pressures and a 30% increase in oxygenation from the use of as little as 3–5 ppm of iNO, and no further benefit from increasing iNO to as high as 80 ppm [139]. However, other studies have failed to show improvements in pulmonary artery pressures, oxygenation, or outcome [140,141]. Future studies are needed to determine the risks, benefits, optimal duration, and impact on survival of iNO in children with severe respiratory disease after heart surgery. The use if iNO in patients with hypoxemic respiratory failure is controversial. Although a transient improvement in
oxygenation is often seen in this setting, the effect is generally self-limited and no effect on mortality has been observed [142] (see Chapter 28 for a further discussion of the use of iNO).

Summary

Neonates, infants, and children with CHD present numerous challenges to the anesthesiologist. These patients commonly have increased myocardial oxygen consumption (e.g., left-to-right shunts, valvular stenosis) and/or decreased myocardial oxygen supply (e.g., cyanosis). CPB has adverse effects on heart and lung function. Less-than-optimal airway management, oxygenation, and/or ventilation can lead to further impairment of oxygen delivery to the heart and other organs with associated injury or death. Patients undergoing thoracic surgery may require SLV in order to optimize surgical conditions. Accordingly, the pediatric cardiovascular anesthesiologist must have knowledge and expertise in managing the airway and ventilation during cardiothoracic surgery.

Selected references

A full reference list for this chapter is available at:
http://www.wiley.com/go/andropoulos/congenitalheart

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CHAPTER 20
Early Tracheal Extubation and Postoperative Pain Management

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Introduction

Today’s medical environment is marked by financial constraints. There is increasing pressure to optimize not only medical care but also resource utilization. This notion has also affected the way we approach the treatment of children requiring surgery for congenital heart disease (CHD). For example, reducing intensive care unit (ICU) and hospital length of stay (LOS) without compromising patient’s safety translates into much-needed cost savings. The following chapter will focus on certain aspects of this approach, also referred to as “fast-tracking.” This term summarizes the various elements of a multidisciplinary approach to efficient patient management, including day of surgery admission, anesthetic management allowing for early tracheal extubation, adequate postoperative pain control, rapid mobilization and hospital discharge.

Background and history

The concept of fast-tracking patients undergoing cardiac surgery was introduced to patient management in the mid-1980s. Diagnosis-related groups were implemented nationally into Medicare reimbursement in the United States in 1983. In an effort to slow down the rapidly increasing costs of providing medical care, this reimbursement model incentivized efficient resource use, and shorter length of ICU and hospital stay was suddenly linked to financial benefits for the hospitals. At the same time, in congenital heart surgery (CHS), extubation at the end of the surgical procedure was almost a necessity, as reliable mechanical ventilators and sedatives with minimal side-effects for small patients were not widely available.

In 1980, Barash et al. published their experience with early extubation in 197 patients less than 3 years of age including neonates; 61% were successfully extubated in the operating room (OR) [1]. The authors noted that “in this era of cost containment, any technique that allows maximal use of resources without jeopardizing patient safety is welcome.” Fast-tracking became popular and eventually routine practice in adults undergoing cardiac surgery in the late 1990s. This was especially true when crowded ICUs slowed the expansion of cardiac surgery programs attempting to gain a share of the increasing number of coronary revascularizations being performed [2]. In 1994, Engelman et al. mentioned the term “fast-track” in their paper, describing a complete care plan for patients undergoing cardiac surgery which was associated with reduced hospital LOS [3].

In the field of CHS, surgical techniques developed rapidly and palliation and repair of CHD in even younger and previously inoperable children became feasible. Reports about favorable effects of a high-dose opioid-based anesthesia emerged in the early 1990s, promising to reduce stress response, morbidity, and mortality [4,5].
Feasibility of fast-tracking in congenital heart surgery

The multidisciplinary approach behind fast-tracking CHS patients typically includes an anesthetic technique that facilitates early tracheal extubation. Early extubation is not consistently defined, and the term is frequently used when the endotracheal tube is removed within 6–8 hours after surgery [8,9]. As mentioned earlier, the feasibility and safety of extubating even young children immediately or soon after complex CHS had already been demonstrated in the early days of CHS, mostly out of necessity [1]. This was accomplished despite the fact that many of the anesthetic agents used at that time are obsolete in today’s practice. Additional reports on early extubation after CHS soon followed. Schuller et al. reported their experience with early extubation in 1984 [10]. In 209 consecutive children undergoing complex open-heart surgery, 88% of those older than 12 months were extubated in the OR. In the same year, Heard et al. published an article on early extubation following CHS in 220 patients, of whom 147 (67%) were extubated in the OR, or within 6 hours of entering the ICU [11]. None of the patients required reintubation. Despite the increasing popularity of a high-opioid anesthetic technique following these early reports, individual centers continued to pursue an early extubation strategy. However, inclusion/exclusion criteria for patients considered for an early extubation strategy, such as patient age and case complexity, vary significantly. While some centers consider early extubation only above a certain age and for simple procedures, others expand such a strategy to the majority of their patients. That early extubation is feasible even in young children [12], complex CHS [13], single-ventricle physiology [14], and those with significant co-morbidities [15] has been demonstrated. Table 20.1 summarizes the current literature on the feasibility of fast-tracking and early extubation in pediatric patients undergoing CHS. Based on the accumulating evidence gathered over the last 30 years, it seems reasonable to conclude that fast-tracking, including early extubation, is feasible and safe in many children undergoing CHS. Factors to be considered in determining who is a good candidate for an early extubation strategy will be discussed in the following section.

Patient selection

While there is good evidence that early extubation and fast-tracking are feasible in many patients undergoing CHS, it seems prudent to have some guidance regarding who is a good candidate for such an approach and who is not. Some preoperative factors are almost universally viewed as contraindications for early extubation after CHS. For example, very few patients who have an endotracheal tube in place before the procedure will be good candidates for such a strategy. However, in many institutions, this practice is further limited to selected patients and based on the anesthesiologist’s or surgeon’s preferences and institutional standards. In many, if not all, of the published reports, specific exclusion criteria were applied, and it is not clear if patients who were not included could have been extubated early as well. The decision to attempt extubation obviously has to be made on an individual basis and is based on many parameters, not all of which are known before the start of the procedure. Contraindications to extubation obviously may apply at the end of surgery, and extubation criteria do not differ from any other patient in whom endotracheal extubation in planned.

There are data, however, demonstrating that some of the information already known preoperatively can be used in planning who is a good candidate for early extubation. Retrospective analyses frequently identify younger age, longer aortic cross-clamp and cardiopulmonary bypass (CPB) times, and high-dose inotrope use associated with deferring endotracheal extubation [16,17].
### Table 20.1: Publications on fast-tracking in children undergoing congenital heart surgery

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study type</th>
<th>Patients enrolled</th>
<th>RACHS category</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barash et al., 1980 [1]</td>
<td>R</td>
<td>197</td>
<td>1–3</td>
<td>• 61% extubated in OR, 11% shortly after ICU arrival, 4% reintubation • Longer CPB time associated with not extubating • Fewer pulmonary complications in early extubation group</td>
</tr>
<tr>
<td>Schuller et al., 1984 [10]</td>
<td>R</td>
<td>209</td>
<td>1–5</td>
<td>• 80% extubated in OR, 2.4% reintubation • Younger age, PAH, and severe preoperative heart failure, associated with not extubating in OR</td>
</tr>
<tr>
<td>Heard et al., 1984 [11]</td>
<td>R</td>
<td>220</td>
<td>1–3</td>
<td>(1 day–16 years)  • 67% extubated in OR or within 6 hours after ICU arrival, no reintubation • Fewer pulmonary complications with early extubation • Longer CPB time associated with prolonged MV</td>
</tr>
<tr>
<td>Burrows et al., 1992 [219]</td>
<td>R</td>
<td>36</td>
<td>1 (ASD only)</td>
<td>• 53% extubated in OR, no reintubation • CPB time associated with early extubation • Shorter ICU LOS in extubated patients</td>
</tr>
<tr>
<td>Laussen et al., 1996 [33]</td>
<td>R</td>
<td>102</td>
<td>1 (ASD only)</td>
<td>• 38% extubated in OR • OR extubation safe • Shorter hospital LOS, and lower costs associated with early extubation</td>
</tr>
<tr>
<td>Heinle et al., 1997 [12]</td>
<td>R</td>
<td>56 (&lt;90 days)</td>
<td>1–6</td>
<td>• 50% extubated in OR or within 3 hours in ICU • 3 patients required reintubation • Patients extubated early had shorter ICU/hospital LOS, reduced costs</td>
</tr>
<tr>
<td>Vricella et al., 2000 [76]</td>
<td>R</td>
<td>201</td>
<td>1–3</td>
<td>• 87% extubated in OR, 94% within 4 hours after surgery, 2.6% required reintubation • Fast-tracking in surgery for CHD is feasible and safe</td>
</tr>
<tr>
<td>Lofland, 2001 [83]</td>
<td>P/O</td>
<td>50</td>
<td>3 (bi–Glenn, Fontan only)</td>
<td>• All patients extubated either in OR or within 1 hour postoperatively • Pain-free spontaneous ventilation resulted in superior hemodynamics</td>
</tr>
<tr>
<td>Neirotti et al., 2002 [13]</td>
<td>R</td>
<td>901</td>
<td>1–3</td>
<td>• 73% extubated in OR, 2.5% reintubation • Younger age, lower weight were risk factors for deferring OR extubation • Simplified postoperative care and increased patient and family satisfaction</td>
</tr>
<tr>
<td>Kloth and Baum, 2002 [34]</td>
<td>R</td>
<td>102 (&gt;2 months)</td>
<td>1–6</td>
<td>• 47% extubated in OR or on ICU arrival, no reintubation • Only RACHS 1–3 extubated early • Mild respiratory acidosis immediately following early extubation well tolerated • Young age, low weight, long CPB time, DHCA, high inotrope use, PAH, among the factors why extubation was not attempted</td>
</tr>
<tr>
<td>Davis et al., 2004 [21]</td>
<td>R</td>
<td>219 (≤36 months)</td>
<td>1–6</td>
<td>• 47% extubated within 24 hours • Age &gt;6 months, no PAH, no CHF, gestational age &gt;36 weeks, associated with early extubation • Intraoperative factors less important, except for cross-clamp time</td>
</tr>
<tr>
<td>Vida et al., 2006 [15]</td>
<td>R</td>
<td>100 (median age 2.5 years)</td>
<td>2 (VSD + PAH only)</td>
<td>• 65% extubated in OR, overall 90% extubated within 6 hours after surgery, two patients extubated early required reintubation • Trisomy 21 and longer CPB time are risk factors for postoperative complications and prolonged MV • PAH not a contraindication for early extubation • Degree of PAH not associated with incidence of postoperative complications, ICU and hospital LOS • Decreased ICU and hospital stay, reduced costs, lower in-hospital mortality with early extubation</td>
</tr>
</tbody>
</table>
In a prospective observational study, Kin et al. found higher procedure complexity classified with the Risk Adjustment for Congenital Heart Surgery (RACHS) score [18], surgery involving aortic cross-clamping, young age, and trisomy 21 to be independent predictors of the decision to not attempt extubation at the end of the procedure [19]. Very few patients in that series failed extubation once attempted. At first glance, these findings seem to classify selection criteria in a very simplified scheme with factors known preoperatively, not accounting for any of the intraoperative factors such as bleeding, cardiac dysfunction requiring high inotropic support, generalized edema, etc., many of which are frequently encountered. However, procedure complexity seems to capture many of these factors. Complex surgeries are frequently associated with longer aortic cross-clamp and CPB times, more pronounced inflammatory response and associated findings such as a higher incidence of bleeding, generalized edema, and higher inotropic requirements, which prohibit early removal of the endotracheal tube all by themselves [20–22].

Aside from complex procedures, young age is one of the most consistently listed reasons for not considering early extubation [19]. In retrospective analyses, young age is consistently associated with not being fast-tracked. Davis et al., for example, assessed factors associated with early extubation following CHS. Children older than 6 months were much more likely to be extubated early compared with younger patients [21]. Winch et al. [23] found that children younger than 3 months were less likely to be extubated early. However, extubation practice varies significantly and even neonates have been extubated successfully immediately after CHS [12]. Age also needs to be assessed in the context of the planned procedure. Certain more complex procedures may be performed at a later time in life, while a simple procedure in an infant may pose a much smaller risk for not qualifying for early extubation. The fact that age alone is not a good selection criterion for fast-tracking is also supported by the published literature. Kin et al. [19], for example found that the relationship between age and attempted OR extubation was inconsistent and not linear. Beyond the age of 2 years however, age did not impact the likelihood of OR extubation. In general, however, it seems that children older than 1–2 months of age are better candidates for early extubation than younger infants. Neonates do not have to be excluded from such a strategy; however, the incidence of encountering contraindications to early extubation at the end of the procedure or soon after in the ICU is typically much higher at this very young age.
Chromosomal abnormalities also account for patients not being considered for early extubation. While not a contraindication *per se*, patients with a genetic variation known to be associated with difficult airway instrumentation, or an increased risk of airway obstruction (e.g. trisomy 21), must be evaluated carefully before attempting early extubation. This is even more of a concern following a long CPB time, which is frequently associated with generalized edema possibly involving the upper airway.

Pre-existing or worsening of pulmonary arterial hypertension (PAH) deserves particular attention. Many practitioners would not attempt early extubation in patients with pre-existing PAH. This practice has been challenged, however, and there are reports of successful extubation following CHS even in patients with significant PAH [15]. In a retrospective analysis on factors associated with early extubation, PAH was not found to be an independent predictor of OR extubation [17], and preoperative PAH did not predict patients who were not extubated in the OR in a similar prospective study [19]. In the latter study, however, significant PAH following CPB was the most common reason for deferring extubation at the end of the procedure. While there is no question that PAH increases the risk for many adverse perioperative events [24–27], it is important to recognize that merely using the current definition of PAH (right-sided pressures >25mmHg) [28] does not accurately reflect such risks in children with CHD [29]. It is often difficult to predict the degree of PAH following surgical repair and, even more importantly, right ventricular failure merely by preoperative right-sided pressures. Assessment of pulmonary vascular resistance (PVR), reactivity to pulmonary vasodilators, as well as the relationship between right-sided pressures and systemic arterial pressure is typically included in the evaluation of PAH in children undergoing CHS [30]. Following weaning off CPB, patients can be reassessed, and even in the setting of pre-existing PAH, patients can often be extubated as long as right ventricular function is adequate and no inhalational pulmonary vasodilators are required.

The likelihood of early extubation following CHS can be better predicted by combining several of the risk factors. Kin et al. developed a risk score model based on factors found to be independently associated with extubation in the OR following surgery [19]. All patients undergoing surgery on CPB without aortic cross-clamp and simple procedures (RACHS 1, e.g. secundum atrial septal defect) were extubated in the OR. Higher RACHS scores and the addition of trisomy 21 as an additional risk factor increased the chance of deferring extubation. Similarly, Davis et al. found age < 6 months, prematurity, congestive heart failure, and pulmonary hypertension to be associated with the chance of failing extubation within 24 hours after surgery. Adding individual factors increased the chance of failing early extubation [21]. Factors associated with early extubation in individual studies can be found in Table 20.1.

**Anesthesia technique**

Despite the fact that certain predictors can help select patients who are good candidates for early extubation even preoperatively, the ultimate decision to attempt extubation will always be deferred to the end of the procedure or ICU. For the purpose of fast-tracking and, in particular, early extubation, an ideal anesthetic would allow early extubation and at the same time provide stable intraoperative hemodynamics, adequate analgesia, and sufficient blunting of the stress response. In the early days of CHS, the use of potent inhalational anesthetics allowed for early extubation at the end of, or within a few hours after, surgery. However, a mainly inhalational anesthetic-based technique is not always tolerated and can be associated with significant side-effects at higher concentrations. An opioid-based anesthetic provides stable hemodynamics and superior suppression of stress response, but typically requires prolonged MV. The addition of a neuraxial anesthetic is advocated by some practitioners and will be discussed in more detail later in this chapter. There are concerns, however, about adequate evidence regarding the safety of a neuraxial technique in the cardiac surgery setting.

Made possible in large part by the introduction of improved and new anesthetic agents such as modern inhalational anesthetics, short-acting opioids, hypnotics and sedatives with favorable pharmacodynamics and pharmacokinetic profiles, all the above-mentioned goals can be accomplished and the side-effects of each individual technique minimized. Such a balanced anesthetic consisting of an inhalational-based technique supplemented with a short-acting opioid is the basis of most modern anesthetic techniques aiming for fast-tracking CHS patients and will be discussed in more detail here.

Patients who qualify for fast-tracking are often admitted on the day of surgery, and frequently intravenous (IV) access has not yet been established. Therefore, an inhalational induction technique with sevoflurane is typically chosen for induction, and is well tolerated in most patients. If true contraindications to an inhalational
induction technique apply, IV access should be established and ketamine or etomidate can be used as induction agents. With a true inhalational-based fast-tracking technique, the inhalational agent is administered throughout the case, including on CPB. The CPB machine must therefore be equipped with a vaporizer. Alternatively, a continuous infusion of IV agents with hypnotic properties can be used during CPB. As a short-acting hypnotic with favorable pharmacokinetic and pharmacodynamics properties, propofol is frequently used during CPB for patients who are fast-tracked [31]. If, however, a decrease in systemic vascular resistance (SVR) must be avoided, a high-dose opioid technique or the use of ketamine should be considered. Ketamine administered as a continuous infusion maintains stable hemodynamics in most CHS patients.

Regarding the IV opioid use, shorter-acting opioids such as fentanyl are preferred. Early extubation can still be accomplished as long as the cumulative dose is limited and larger repetitive doses avoided towards the end of the procedure. Frequently, not more than 5–10 μg/kg fentanyl is given for the whole case [17,32–34], which is significantly less than the doses used for a high-dose opioid technique. Remifentanil is an ultra-short-acting opioid that is metabolized by non-specific esterases in plasma and tissues and minimally affected by CPB [35]. Due to its rapid elimination, it is an ideal agent for fast-tracking CHS patients. The use of remifentanil allows conduction of a high-dose opioid anesthetic with the benefits of reducing stress response, but with a fast recovery facilitating early extubation [36–38]. The challenge is to provide adequate analgesia after an infusion of remifentanil is discontinued due to its rapid elimination. A neuraxial technique, non-opioid analgesics, and dexmedetomidine can be very helpful for this purpose.

Dexmedetomidine is a sedative agent that confers sedation by selectively binding to central α2 adrenoceptors. Respiratory indices and upper airway patency are maintained during dexmedetomidine sedation in children [39–42]. In addition to sedative and analgesic-sparing effects, dexmedetomidine use has also been reported to reduce stress response in patients undergoing cardiac surgery [43]. Additional favorable properties supporting dexmedetomidine’s role in the fast-tracking setting are the reduced incidence of emergence delirium after inhalational anesthesia in children [44–46] and its possible role in reducing the incidence and even treatment of arrhythmias [47]. Because of these favorable properties, dexmedetomidine is even used throughout the case by some practitioners and allows the reduction of opioid requirements for fast-tracking purposes. Undesirable hemodynamic effects of dexmedetomidine such as brady-cardia, hypotension and hypertension, decrease in cardiac output [48], as well as an increase in PVR, especially with high doses or fast bolus administration, have all been described. These side-effects however, are highly dose- and age-dependent. Typically, dexmedetomidine is well tolerated in older children [49]; however, few data are available regarding safe doses in infants and particularly in neonates. There are data showing that dexmedetomidine clearance in neonates and infants is reduced [50–51], and accumulating drug levels causing bradycardic side-effects may occur. Until the safety of dexmedetomidine has been established, many practitioners either avoid it or reduce doses in these very young age groups. It must also be noted that at this point dexmedetomidine is only approved by the US Food and Drug Administration (FDA) for use in adults for ICU sedation up to 24 hours. Despite this, dexmedetomidine has been widely used in children even for prolonged periods of time [52].

In summary, fast-tracking and early extubation are facilitated by modern anesthetic agents combined with strategies to provide good analgesia without significant respiratory depression.

**KEY POINTS: ANESTHESIA TECHNIQUE**

- A balanced, inhalational anesthetic-based anesthetic technique is usually chosen for fast-tracking.
- Opioid use is limited, and short-acting opioids are preferred.
- Non-opioid analgesics and opioid-sparing drugs such as dexmedetomidine are used to reduce opioid use.
- Neuraxial techniques can supplement pain management, but their use is controversial.

**Surgery and CPB considerations**

Surgical and CPB techniques contribute significantly to the ability to fast-track patients, and have an impact on anesthetic management. Aside from the quality of the surgical repair, it is increasingly recognized that outcomes can be improved by reducing the inflammatory response [53] and limiting surgical trauma.[54] For example, avoiding or limiting prolonged periods of deep hypothermia [55] and circulatory arrest [56] reduces CPB time and associated complications such as cardiac dysfunction, coagulopathy, and transfusion requirements [57]. Limiting the inflammatory response results in less generalized edema and improves pulmonary function [58–60], all important components to successfully fast-tracking CHS patients. Minimally invasive surgical techniques [61–63], hybrid procedures [64], or alternate surgical access for selected CHD [65] can further contribute to limiting surgical trauma.

Significant changes have also been made to CPB and perfusion techniques. These improvements often benefit patients who are considered for fast-tracking, and include miniaturized CPB circuits [66], beating heart surgery
Techniques [67], less cooling and pulsatile CPB [68], and selective perfusion strategies [69]. Modified ultrafiltration (MUF) is also frequently part of a fast-tracking protocol and has been shown to decrease edema, and improve pulmonary and cardiac function [70, 71]. Immediate effects on hematocrit and coagulation also help with fast-tracking [72]. Many of these techniques are controversial and not universally practiced, however, and the safety and possible outcome benefits are still being evaluated. Nevertheless, many of the currently ongoing changes to the practice of CHS promise to be beneficial to fast-tracking.

**KEY POINTS: SURGERY AND CPB CONSIDERATIONS**

- Surgical and CPB techniques contribute significantly to fast-tracking.
- Measures to reduce inflammatory response are key to the ability to fast-track.
- Selective perfusion techniques avoid prolonged periods of circulatory arrest and profound cooling.

**Failed extubation and prolonged mechanical ventilation**

It must be noted that selection criteria for patients who are good candidates for fast-tracking and early extubation are not necessarily the same as the factors associated with extubation success and/or prolonged MV. Selection criteria that were discussed earlier can help guide physicians in planning an anesthetic, and based on prior studies, properly selected patients will fulfill extubation criteria in a majority of cases. However, assessment of extubation criteria, and the decision to remove the endotracheal tube can only be made at the end of the procedure or in the ICU immediately prior to the planned extubation. Neuromuscular blockade must be reversed or dissipated and should be documented with use of a nerve stimulator or definite clinical criteria (i.e., leg lift or head lift for >5 seconds). Pressure or volume support modes available on modern anesthetic machine ventilators, if utilized, should minimize the support provided during assisted breaths. Arterial blood gas values and peripheral oxygen saturation should demonstrate minimal alveolar-to-arterial oxygen tension gradient where applicable in acyanotic patients. Extubation success is only obvious once the patient is able to sustain spontaneous ventilation without significant respiratory support. And if a patient fails extubation or extubation was never attempted and requires prolonged ventilatory support, certain factors have been found to be associated with prolonged MV. These considerations will be discussed in more detail here.

If early extubation was planned but not attempted, the anesthesiologist together with the surgeon will have made this decision based on subjective as well as objective observations and findings. In general, extubation criteria have been defined, are relatively consistent between practitioners and often follow specialty society guidelines and recommendations, and they are not different in the CHS setting. However, the reasons for deciding to proceed with attempting extubation may vary greatly between institutions. In a prospective observational study, almost all patients presenting for CHS who did not require mechanical support preoperatively were considered as candidates for extubation at the end of the surgery [19]. The authors further assessed the factors that made the practitioners decide not to attempt extubation immediately following surgery. Significant pulmonary hypertension following CPB, hypoxemia, bleeding/coagulopathy, airway compromise (edema), insufficient respiratory effort, hyperthermia, and open chest were listed by the practitioners as the main reasons for diverting from the original plan to remove the endotracheal tube at the end of the procedure.

Preisman et al. listed hemodynamic instability, open chest, hypoxemia, hyperlactemia, inadequate urine output, and higher transfusion requirements as reasons why patients were excluded from planned early extubation [32], while Kloth et al. [34] listed young age, low weight, significant co-morbidity, preoperative MV, high inotropic support, ongoing bleeding, airway concerns, significant PAH, and nitric oxide use.

Once the endotracheal tube is removed, extubation success is relatively high in most studies. Extubation failure is often defined as reintubation within 96 hours after extubation [73, 74]. Reintubation rates reported in patients following fast-track CHS do not differ from those in children who were not fast-tracked, or from any other major surgery setting, and typically do not exceed 4% in the majority of published studies [13, 14, 17, 75, 76]. A recent review of the literature and meta-analysis confirmed these findings, and reintubation rates did not differ between patients who were extubated early vs. late [9]. In neonates and very young infants, however, extubation failure and reintubation may be higher [12].

Reasons for reintubation and factors associated with failed extubation have been listed by several investigators. Harrison et al. performed a retrospective chart review and analyzed for independent predictors of reintubation within 24 hours after extubation in children aged 3 years or younger undergoing CHS [22]. Reintubation was required in 22 out of 219 surgeries, and trisomy 21, surgery with deep hypothermic circulatory arrest, and pulmonary hypertension as the strongest predictor were independently associated with failed extubation. Gupta et al. [74] evaluated extubation failure in infants undergoing the Norwood operation. Pulmonary complications, cardiac dysfunction, diaphragmatic paralysis, and airway-related complications were the most common reasons why patients required reintubation. Almost identical causes of extubation failure were found in patients undergoing...
repair for tetralogy of Fallot [73]. Another study evaluating extubation success following CHS found lung mechanics and associated abnormalities of respiratory function, such as increased work of breathing, as the main cause for failing extubation [77]. Other factors frequently identified as reasons why patients fail extubation are neurologic complications, cardiovascular insufficiency, poor oxygenation, and respiratory acidosis [78]. When evaluating reintubation rates, it must be recognized that reintubation may be required for reasons other than not sustaining spontaneous ventilation. This is not failure of an early extubation strategy per se. These patients would have been successfully extubated, but required reintubations for other reasons, such as return to the OR for surgical intervention, sepsis, or pneumonia, and thus, in the context of fast-tracking, reported reintubation rates have to be interpreted accordingly.

The decision to continue MV in patients following surgery for a few hours or until the next day is often based on institutional preferences. Prolonged MV, however, often defined as MV beyond the third postoperative day, is usually secondary to a more complicated postoperative course. A prospective observational study found factors associated with prolonged MV to be inconsistent and heterogeneous, and included pulmonary hypertensive events, delayed sternal closure, peritoneal dialysis, pulmonary complications, low cardiac output syndrome, neurological events, nitric oxide use, and tracheomalacia [20]. In a retrospective analysis, independent risk factors of prolonged MV were surgical complexity assessed with the RACHS score, nosocomial pneumonia, low cardiac output syndrome, postoperative positive fluid balance, and extubation failure [79]. Phrenic nerve injury, pleural effusions, pulmonary hypertension, and other airway complications are typical pulmonary complications that require prolonged MV [80]. Trisomy 21 is also frequently associated with a more complicated postoperative course, including prolonged MV [81].

Box 20.1 summarizes common reasons for deferring planned extubation, early extubation failure, and prolonged MV following CHS.

<table>
<thead>
<tr>
<th>KEY POINTS: FAILED EXTUBATION AND PROLONGED MV</th>
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<tr>
<td>• Deferring planned extubation to a later time point is different from failed extubation.</td>
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<tr>
<td>• Extubation criteria do not differ from patients who are not fast-tracked.</td>
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<tr>
<td>• Reintubation rates in fast-tracked and conservatively managed children are comparable.</td>
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<tr>
<td>• Prolonged MV beyond the third postoperative day is unrelated to fast-tracking, and associated factors comprise a wide spectrum of complications associated with CHS.</td>
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**Box 20.1:** Common reasons for deferring early extubation, extubation failure, and prolonged mechanical ventilation in patients undergoing congenital heart surgery

**Common reasons for deferring planned early extubation**
- Preoperative mechanical ventilation
- Pulmonary hypertension (pre- and post-CPB)
- Pulmonary hypertension requiring nitric oxide
- Insufficient respiratory effort
- Airway compromise, generalized edema
- Hypoxemia
- Hemodynamic instability (high inotrope use, hyperlactemia, open chest, ECMO, hemodynamically significant arrhythmia)
- Ongoing coagulopathy, increased transfusion requirements
- Long CPB, aortic cross-clamp time, DHCA
- Young age, low weight
- Hypothermia
- Inadequate urine output
- Chromosomal abnormalities (e.g. trisomy 21)

**Common reasons for failed early extubation**
- Pulmonary hypertension
- Cardiovascular instability
- Ongoing coagulopathy
- Pulmonary: Insufficient respiratory effort, increased work of breathing, hypoxemia
- History of trisomy 21
- Phrenic nerve paralysis
- Pleural effusion
- Other complications requiring surgical intervention

**Reasons for prolonged mechanical ventilation (>72hrs) following CHS**
- Pulmonary hypertension (particularly nitric oxide use)
- Pulmonary complications, pneumonia, phrenic nerve injury, tracheomalacia
- Neurologic complications
- Hemodynamic instability, low cardiac output syndrome, low urine output requiring dialysis
- Open sternum

CPB, cardiopulmonary bypass; ECMO, extracorporeal membrane oxygenation; DHCA, deep hypothermic circulatory arrest.

**Benefits of fast-tracking**

The benefits of fast-tracking were noticed even in the early days of CHS when extubation at the end of a procedure was done more out of necessity than by choice. In 1979, Barash et al. noted fewer complications from MV, earlier patient mobilization, increased patient and parent satisfaction, and optimal resource use with possible cost benefits [1]. Further reports on early extubation in pediatric cardiac patients followed, and the increasing experience with this approach led to recognizing and reporting of possible benefits in this patient population. Many of the initially reported benefits are still valid today, and even though modern ventilator technology has significantly improved,
avoiding prolonged periods of MV is usually preferred. Patients without MV typically require less sedation, which often leads to lower inotropic (hemodynamic) support, more rapid patient mobilization, decreased ICU and hospital LOS, and possibly decreased costs [13,32,82]. Aside from cost savings, prolonged hospital stay can increase the risk of hospital-acquired complications such as infections. The risk of hospital-acquired infections cannot be underestimated and is one of the main reasons why fast-tracking has been adopted, particularly in some of the developing countries with a higher surgical wound infection rate. Additionally, early extubation allows earlier mobilization and verbal communication between the child, parents, and hospital staff involved. Consequently, patient and parent satisfaction is increased in children who are extubated in the OR, or soon after ICU arrival. A large meta-analysis on early extubation in CHS even found lower in-hospital mortality, as well as a trend towards shorter ICU and hospital LOS, lower costs, and fewer respiratory complications in patients who were extubated early; however, it is not clear if selection bias can partially explain these findings [9]. Benefits found with early extubation are listed in Table 20.1 and Box 20.2.

Box 20.2: Benefits associated with fast-tracking and early extubation
- Fewer ventilator-associated complications, e.g.:  
  - Accidental extubation  
  - Laryngotracheal trauma  
  - Mucous plugging of endotracheal tube  
  - Pulmonary hypertensive crisis from endotracheal suctioning  
  - Barotrauma from positive pressure ventilation  
  - Ventilator-associated pulmonary infections and atelectasis  
- Reduced requirements for sedatives/analgesics  
- Greater hemodynamic stability  
  - Beneficial effects of spontaneous ventilation in stage 2 & 3 single-ventricle palliation  
  - Lower inotrope use  
- More rapid patient mobilization  
  - Earlier ICU discharge  
  - Decreased hospital length of stay  
- Reduced costs  
- Greater parent and patient satisfaction

Certain types of CHS patients may benefit more than others from fast-tracking, and in particular from early extubation and spontaneous ventilation. In patients with single-ventricle physiology undergoing bi-directional Glenn or Fontan procedure, early extubation and spontaneous ventilation have been associated with improved hemodynamics [14,83]. Lower intrathoracic pressure associated with spontaneous ventilation increases central venous blood return, which becomes the driving force of pulmonary blood flow across the pulmonary vascular bed and thus for maintaining left ventricular preload and cardiac output [84,85]. In a study of 50 patients undergoing either bidirectional Glenn or Fontan operation who were extubated either in the OR or within 1 hour postoperatively, decreased pulmonary artery pressure and increased cardiac index were recorded following extubation [83]. Morales et al. [14] found mean pulmonary artery and atrial pressure to be lower and mean arterial blood pressure to be higher in patients who were extubated soon after surgery. In patients who were extubated in the OR, less inotropic support was required, the time to chest tube removal was shorter, and ICU/hospital stay and costs were reduced. In particular, in patients following a bidirectional Glenn surgery, mild hypercapnia frequently seen following early extubation should increase blood flow to the SVC and pulmonary circulation from cerebral vasodilation [86–88]. Hoskote et al. investigated the systemic and pulmonary hemodynamic effects of different CO₂ tensions in patients following bidirectional Glenn anastomosis in a prospective trial [89]. Mild hypercarbia (PaCO₂ up to 55 mmHg) resulted in improved systemic oxygenation, increased systemic (Qp) and pulmonary (Qp) blood flow (Qp/Qs unchanged), increased cerebral blood flow, and decreased systemic vascular resistance (SVR). PVR remained unchanged in this study. In another retrospective study in children following right heart bypass surgery, early extubation and spontaneous ventilation resulted in decreased PVR, lower mean pulmonary artery pressure, and fewer pulmonary complications such as pneumonia and atelectasis [84]. Despite the findings showing that mild permissive hypercapnia may be beneficial or at least well tolerated in patients following bidirectional Glenn and Fontan procedures, there still remains widespread concern and controversy about the safety of fast-tracking and early extubation in this patient population, particularly as the age of bidirectional Glenn patients continues to decrease and is often 2–3 months [90].

Cost containment in healthcare has become more important than ever and centers caring for children with CHD are not exempt from this. The strongest predictors of costs for patients undergoing cardiac surgery are usually intensive care and hospital LOS, OR time, and postoperative complications. Any technique resulting in earlier patient discharge without compromising patient’s safety should therefore result in cost savings. While many studies in patients undergoing CHS have shown a decrease in ICU and hospital LOS, as well as cost savings from shorter time on MV [9,12,14,15], overall cost benefits from fast-tracking and early extubation are not easily evaluated. Most studies reporting on cost savings acknowledge difficulties in comparing historical control groups with contemporary patient care. Results from randomized studies in adult cardiac surgery, however, clearly demonstrated cost benefits from fast-tracking patients [91–93]. Most of those studies conclude that fast-tracking results in shorter ICU and hospital LOS, and decreases in resource use, all of which led to decreased costs. While it may be difficult to compare costs between different institutions and patient populations, it is quite likely that at least some of these findings can be extended to CHS. Heinele et al. [12], for example, found significant cost reductions in patients who
were extubated early due to shorter ICU/hospital stay. Vida et al. showed that patients who were extubated early had significantly shorter ICU and hospital stay, and every additional day spent on the ICU increased overall costs of the procedure by 10% [15]. In patients undergoing atrial septal defect repair, for example, Laussen et al. found similar ICU charges regardless of time of extubation; however, combined ICU and OR charges were reduced mainly because of avoidance of postoperative MV [33].

Most of these reports on cost savings are based on retrospective analyses and are not from randomized, contemporary matched patient populations. When comparing costs using a historic control group, additional factors such as experience of the surgeon, inflation, and increased costs due to new technologies have to be considered and are almost impossible to accurately account for. Lawrence et al. [94] compared their single institution experience of implementing fast-tracking with outcomes from a large contemporary nationwide database for the same time periods. When fast-tracking including early extubation (the goal was to extubate at the end of the procedure in the OR) was fully implemented, the median hospital LOS at their institution decreased by 1 day compared with the earlier time period, while nationally LOS remained unchanged. This translated into significant cost savings (33% and 35% for atrial and ventricular septal defects, respectively), whereas an increase in costs was noted nationally for the repair of both congenital heart defects in the same time period. A multiple regression analysis confirmed the decrease in both LOS and costs to be significantly greater at their institution compared with the nationwide database. Hospital mortality and 2-week readmission rates were unchanged and were not different from the national rates. This is particularly important, as an increase in postoperative complications associated with fast-tracking and early extubation would outweigh the potential cost-saving benefits.

Early extubation is only one element in the multidisciplinary approach to fast-tracking CHS patients. A meta-analysis of randomized, controlled trials on fast-tracking in patients undergoing coronary artery bypass grafting (CABG) showed that standardized perioperative care including an early extubation protocol and not just early extubation per se was essential in reducing ICU and hospital LOS [95]. Avoiding postoperative complications such as bleeding, arrhythmias, cardiogenic shock, and renal failure is essential.

**KEY POINTS: BENEFITS OF FAST-TRACKING**

- Many of the benefits associated with fast-tracking are related to earlier patient mobilization, and shorter ICU and hospital LOS.
- Reducing hospital-acquired infections by reducing LOS is one of the main reasons for implementing fast-tracking, particularly in developing countries.
- There are increasing data supporting the proposition that fast-tracking reduces costs.

**Concerns and safety of fast-tracking**

While fast-tracking and early extubation can certainly be accomplished in children undergoing CHS, the debate continues as to whether such an approach is safe and whether it offers benefits over a traditional approach [90,96]. The individual patient’s response to CPB is unpredictable. The release of inflammatory mediators, severity of lung injury, and changes in PVR are among many of the factors frequently cited in the discussion regarding early extubation. It must be noted, though, that improvements in CPB technique help to reduce the inflammatory response. Additionally, modern anesthetic agents, including short-acting opioids, allow for adequate blunting of inflammatory mediator release without compromising an early extubation strategy. Concerns about the lack of data from randomized prospective studies showing clear benefits of fast-tracking and early extubation add further to the controversy. Some of the controversy comes from the poorly defined definition of fast-tracking and early extubation. Early extubation is typically part of a fast-tracking approach to patient care with defined goals. However, this does not imply compromising patient safety, which has been clearly demonstrated in adult cardiac surgery where fast-tracking is almost uniformly practiced. Early extubation should be viewed as reducing unnecessary time on MV, rather than removing the endotracheal tube regardless of the underlying patient’s condition. Commonly acknowledged extubation criteria, including adequate lung mechanics and oxygenation, and hemodynamic stability also apply to patients who are considered candidates for fast-tracking and early extubation. This is regardless of whether the endotracheal tube is removed at the end of procedure in the OR, or after a certain time in the ICU. For example, low cardiac output and decreased left ventricular function following CPB is usually considered a contraindication for early extubation. MV decreases oxygen consumption and workload of the heart and is considered beneficial by many practitioners in this setting. If responsive to low inotropic support, however, mild cardiac dysfunction does not need to be an absolute contraindication for early extubation and many of these children can be fast-tracked.

At this point, there is good evidence from multiple retrospective [12,13,17,76] as well as prospective observational studies that fast-tracking can be accomplished safely even in CHS. Preisman et al. randomly allocated 100 consecutive children (aged 1 month to 15 years) presenting for CHS to an anesthetic management aiming for fast-tracking and OR extubation or to a traditional approach with elective postoperative prolonged MV [32]. There was no significant difference in mortality, reintubation rate, reoperation for bleeding, infection, and other miscellaneous complications. The authors do acknowledge, though, that the study was not adequately powered to conclusively comment on the safety of fast-tracking, something that could only be accomplished with a large multicenter study. A meta-analysis of available studies on early extubation...
concluded that early extubation is associated with lower ICU and hospital LOS without increased morbidity or mortality [9]. Another measure of the safety of early extubation in CHS is the reintubation rate. As mentioned earlier, reintubation rates reported in the literature are low, and do not differ from those in patients who are not fast-tracked. Mild hypercapnia and respiratory acidosis frequently seen with early extubation are generally well tolerated [16,33,34]. Additionally, hospital readmission rates and mortality need to be considered when assessing safety of fast-tracking CHS patients. Laurence et al found no significant change in hospital mortality, and 2-week readmission rates were unchanged after implementing fast-tracking at their institution and were not different from the reported national rates [94].

**KEY POINTS: CONCERNS AND SAFETY OF FAST-TRACKING**

- Published data on fast-tracking support the safety of this strategy in CHS as well.
- Reintubation and readmission rates are similar to non-fast-tracked patients.
- Side-effects of early extubation, such as mild hypercapnia, are usually transient and well tolerated.

**Postoperative considerations**

The multidisciplinary approach required for the success of fast-tracking CHS patients is particularly important in the postoperative arena, and the individual roles of all team members cannot be overemphasized. In general, standard postoperative considerations also apply to CHS patients who are fast-track and include adequate pain control and sedation without compromising respiratory parameters. For the purpose of fast-tracking, patients should be extubated within a few hours after ICU arrival unless contraindications to extubation apply. Pain management following CHS is part of any anesthetic regimen and a vital component of fast-tracking. Adequate pain control without compromising respiratory effort shortly after surgery is key to the success of an early extubation strategy. While a detailed review of pain management in surgical patients goes beyond the scope of this review, strategies frequently used in fast-tracking CHS patients will be presented. Pain management strategies usually combine IV and regional or even neuraxial techniques, which will be discussed in more detail below. Intravenously administered opioids have been the mainstay of any pain regimen following surgery, including patients who are fast-tracked. More recently, IV acetaminophen has been added to the armamentarium of intravenously administered drugs [97]. It is currently FDA-approved for use in children older than 2 years [98], but off-label use in younger children is almost ubiquitously practiced. Acetaminophen use for pain control seems attractive for fast-tracking as it does not cause respiratory depression, hemodynamic instability, platelet dysfunction, or potential kidney injury. However, there is currently limited experience with parenteral application in the pediatric cardiac surgery setting in the US [99]. Hepatic injury is a known serious side-effect, and pediatric dosing and contraindications should be carefully considered. Systemic clearance in neonates and young infants is significantly reduced. Dose reductions of 33% (age 1 month to <2 years), and 50% in neonates up to 28 days, are recommended by the manufacturer. Other IV non-steroidal anti-inflammatory agents, such as ketorolac and indomethacin, have been linked to side-effects such as gastrointestinal bleeding, bronchospasm, and kidney injury, which is why their use is somewhat restricted in the cardiac surgery setting. In a small study in children undergoing CHS, however, the use of ketorolac was not associated with adverse events [100]. The use of dexmedetomidine has been discussed earlier and typically reduces opioid requirements. Dexmedetomidine has also been used for sedation in children following CHS [101–104]. It allows for sedation without significant respiratory depression and seems ideal for the purpose of fast-tracking. It must be noted, however, that dose-finding studies establishing the safety of its use in children and, in particular small infants and neonates, are mostly missing at this point. In clinical practice, dexmedetomidine maintenance doses usually range from 0.1 to 0.8 μg/kg/hour, with reduced doses in the very young. Bolus administration is controversial, and typically up to 1 μg/kg is administered prior to a continuous infusion. Frequently, practitioners will also reduce the bolus dose in the very young or omit bolus administration altogether.

In the setting of fast-tracking, it is particularly important to differentiate between emergence delirium or agitation and inadequate pain control in order to avoid too large doses of respiratory depressive drugs compromising the success of early extubation. The addition of benzodiazepines in this context and for consequent sedation in the ICU in patients who are fast-triggered is common practice. While the goal of adequate pain control and sedation without respiratory depression is clearly defined, no treatment option is devoid of side-effects and consequently pain management often varies between institutions and practitioners.

A mild respiratory acidosis is frequently encountered in children who have been extubated early. This is typically well tolerated, normalizes within a few hours, and reintubation for respiratory depression is rarely necessary [14,17,33,34,75,76]. In case of mild airway obstruction or diminished respiratory effort, non-invasive respiratory support such as nasal continuous positive airway pressure (CPAP) can be advantageous for a few hours following extubation. The use of CPAP preserves the advantages of spontaneous ventilation and helps avoiding reintubation.
**Neuraxial techniques**

The addition of neuraxial techniques for pain management is advocated by some practitioners, while others vehemently oppose any neuraxial manipulation in patients undergoing CHS with CPB and full heparinization [105,106]. Concerns about the safety of neuraxial manipulation in patients who are subsequently fully heparinized prevail. Nevertheless, there is evidence that a neuraxial technique can be used safely and may offer benefits in the cardiac surgery setting. Epidural (including caudal) as well as intrathecal, single-shot, and continuous catheter techniques are frequently used. While a thorough review of the individual techniques would go beyond the scope of this text and has been presented in detail elsewhere [107,108], each individual technique will be discussed in relation to benefits, concerns, and evidence regarding safety and outcome in the pediatric cardiac surgery setting. The use of neuraxial anesthesia in CHS studies are presented in Table 20.2. As data on the safety in patients undergoing CHS are limited, references from large prospective studies in the adult cardiac population providing further insight into the matter are also included in the following sections.

**Single-shot neuraxial techniques**

Single-shot neuraxial techniques offer the advantage of simplicity and avoidance of manipulating a catheter in the epidural space. Single-shot spinal and, in younger children, epidural (caudal) techniques are frequently used. For procedures at the thoracic level, large volumes and higher doses of local anesthetics are required to reach an adequate level from a caudal approach [109]. Sufficient analgesic levels with single-shot local anesthetic administered from the caudal level are only maintained for a short time period, and certainly not far into the postoperative period. Consequently, single-shot caudal techniques are almost always combined with an opioid; most commonly, more hydrophilic opioids and, in particular, preservative-free morphine. Morphine administered via the caudal space exhibits its peak analgesic effect within 4–7 hours [110] and its duration of action has been reported up to 24 hours [111,112]. Typically, up to 100 μg/kg of preservative morphine is administered into the caudal space, with dose adjustments in the very young. The analgesic effect of caudally administered morphine varies, however, and is somewhat less predictable than a single-shot intrathecal technique. This is probably due to septations in the caudal epidural space, and a higher failure rate mostly from inadvertent subcutaneous rather than epidural injection [113]. In older children, a single-shot subarachnoid injection of preservative-free morphine (5–10μg/kg) can easily be accomplished. In general, epidurally and intrathecally administered opioids have been shown to provide excellent analgesia [114,15], to blunt the stress response to surgery and CPB [116,117,118], improve pulmonary function [119] and reduce time on MV [120,109]. The use of intrathecal local anesthetics in children undergoing cardiac surgery, including high spinal anesthesia, has been described [114]. Hypotension is less frequently observed than adult spinal anesthesia [121]; however, the duration of the block for pain management is usually inferior to an epidural continuous technique and is thus very infrequently practiced [114]. In addition to the already discussed use of local anesthetics and opioids, α2-receptor agonists such as clonidine [122–124], and more recently dexmedetomidine [125,126], ketamine [127,128], and magnesium [129–132], have all been added in an effort to minimize side-effects from neuraxially administered opioids, such as respiratory depression, and to prolong analgesic effects. A systematic review of the current literature identified 20 randomized trials where clonidine had been added to local anesthetic for caudal regional anesthesia [133]. The addition of clonidine resulted in superior longer lasting pain control and fewer patients requiring rescue analgesics, with no significant difference in complications. A similar review with ketamine added to caudal local anesthetics produced similar findings; however, the authors also indicated that the available data do not allow for conclusions regarding potential neurotoxic effects [134]. To date, the experience in the US with these additives remains limited and they are not routinely used. Even though single-shot techniques may provide somewhat inferior pain control when compared with a thoracic epidural catheter technique, they are quite popular among many practitioners as single-shot techniques require less time and the potential risks associated with an indwelling catheter are avoided [135].

**Catheter-based neuraxial techniques**

Epidural catheter insertion for pain management in children undergoing CHS has been described. Similarly to single-shot neuraxial techniques, however, there are concerns about the safety in the cardiac surgery setting. Consequently, while individual centers routinely use epidural catheters and report good outcomes in the CHS setting, others object to epidural catheter manipulation in this patient population. Regardless of this ongoing controversy, lumbar epidural, caudal epidural, thoracic epidural, paravertebral, and even subarachnoid catheter insertion [136] have been reported in children undergoing cardiac surgery [75]. Compared with single-shot neuraxial or IV analgesia, epidural catheter techniques promise superior analgesia [137]. Peterson et al., for example, compared caudal epidural, lumbar epidural, thoracic epidural, and intrathecal blocks using a combination of morphine or hydromorphone and local anesthetic [75]. The majority of patients were extubated in the OR, and the use of a thoracic epidural catheter technique provided superior pain control with overall fewer adverse events
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study type</th>
<th>Patients enrolled</th>
<th>Neuraxial</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shayevitz et al., 1996 [139]</td>
<td>R</td>
<td>27/27</td>
<td>• Lumbar epidural catheter morphine infusion, vs. IV opioid</td>
<td>• Shorter time to extubation, shorter ICU LOS, and earlier enteral feeding in epidural group</td>
</tr>
<tr>
<td>Rosen &amp; Rosen, 1989 [112]</td>
<td>P/R</td>
<td>32 (2–12 years)</td>
<td>• Caudal morphine (75 µg/kg)</td>
<td>• Lower pain scores and less supplemental IV morphine in caudal group</td>
</tr>
<tr>
<td>Hammer et al., 2000 [137]</td>
<td>R</td>
<td>25/25</td>
<td>• Single-shot intrathecal morphine (7–10 µg/kg) + tetracaine, vs.</td>
<td>• 100% extubation in OR in both groups, no reintubation</td>
</tr>
<tr>
<td>Peterson et al., 2000 [75]</td>
<td>R</td>
<td>220</td>
<td>• Single-shot epidural, intrathecal, and epidural catheter techniques</td>
<td>• Patients with single-shot required more sedative/analgesics</td>
</tr>
<tr>
<td>Rojas-Perez et al., 2003 [109]</td>
<td>P/R</td>
<td>15/15</td>
<td>• Caudal (bupivacaine + morphine) + GA, vs. GA alone</td>
<td>• 89% extubated in OR, eight reintubations</td>
</tr>
<tr>
<td>Finkel et al., 2003 [121]</td>
<td>P</td>
<td>30 (7months–13 years)</td>
<td>• Intrathecal tetracaine + morphine</td>
<td>• Shorter time to extubation in caudal group</td>
</tr>
<tr>
<td>Suominen et al., 2004 [144]</td>
<td>P/R/observer-blinded</td>
<td>35/36</td>
<td>• Intrathecal morphine (20 µg/kg) + GA, vs. GA alone</td>
<td>• Less intraoperative fentanyl requirement in caudal group</td>
</tr>
<tr>
<td>Humphreys et al., 2005 [136]</td>
<td>P/R</td>
<td>30/30 (&lt;2years)</td>
<td>• Intrathecal catheter (24–48 hours) morphine (20 µg/kg) and bupivacaine + GA, vs. GA alone</td>
<td>• Good hemodynamic stability with spinal anesthesia</td>
</tr>
<tr>
<td>Hammer et al., 2005 [137]</td>
<td>P/R</td>
<td>20/20</td>
<td>• Single-shot intrathecal morphine (7 µg/kg) + GA, vs. GA alone</td>
<td>• Time to first IV narcotic dose longer, and total dose of IV morphine lower in intrathecal group</td>
</tr>
<tr>
<td>Leyvi G et al., 2005 [120]</td>
<td>R</td>
<td>46/71</td>
<td>• Single-shot caudal (bupivacaine + 70–110 µg/kg morphine), vs. GA alone</td>
<td>• No difference in time to extubation and ICU LOS</td>
</tr>
<tr>
<td>Stuth et al., 2011 [145]</td>
<td>P/R/observer-blinded</td>
<td>64 (2–55months) Stage 2 and 3 single-ventricle palliation</td>
<td>• Caudal group (100 µg/kg + bupivacaine), vs. Control (placebo caudal) + postoperative IV morphine</td>
<td>• Spinal anesthesia resulted in lower plasma norepinephrine, epinephrine, and lactate levels</td>
</tr>
<tr>
<td>El-Morsy et al., 2012 [215]</td>
<td>P/R/observer-blinded</td>
<td>60 (1–24 months)</td>
<td>• Thoracic epidural, vs. Paravertebral catheter</td>
<td>• Lower pain scores in intrathecal group</td>
</tr>
<tr>
<td>Nasr et al., 2013 [125]</td>
<td>P/R/observer-blinded</td>
<td>20/20</td>
<td>• Caudal bupivacaine + dexmedetomidine (0.5 µg/kg), vs.</td>
<td>• No difference in adverse events</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Caudal bupivacaine + fentanyl (1 µg/kg)</td>
<td>• No difference in ICU/hospital LOS and pain score</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Shorter time to extubation and reduced time on mechanical ventilation in caudal group</td>
</tr>
</tbody>
</table>

R, retrospective; P, prospective; O, observational; GA, general anesthesia; ICU, Intensive Care Unit; OR, Operating Room; LOS, length of stay.
compared with other neuraxial techniques. It seems logical that injection at the thoracic level results in better analgesia for cardiac surgery, and catheter manipulation is minimized. Additionally, local anesthetic administration at the thoracic level provides the additional advantage of sympathetic blockade and superior blunting of stress response otherwise not achieved by lower epidural single-shot opioid-only based techniques. The insertion of an epidural catheter at the lumbar or caudal level and advancement of the catheter cranially in order to achieve adequate blockade at the thoracic level are also being practiced [138–143]. While this technique seems to offer the advantage of not manipulating a needle in the thoracic epidural space, the epidural canal is heavily vascularized and the risk of advancing a catheter over a longer distance may actually carry a higher risk of injuring an epidural vein compared with the thoracic approach. Also, the correct positioning of the catheter tip at the thoracic level is not always achieved without fluoroscopy and may explain why catheters placed in the thoracic region seem to provide superior pain control with fewer side-effects. While there may be real and potential benefits to neuraxial catheter-based analgesia compared with an IV analgesic regimen, the logistics associated with epidural catheter insertion and management are significantly more complex. Unlike adults, children usually do not tolerate awake catheter insertion. Day-of-admission surgery is routinely performed in the US and is part of fast-tracking CHS patients, preventing catheter insertion well ahead of surgery and systemic heparinization. Additionally, catheter removal in patients with ongoing coagulopathy after surgery is problematic. Even in patients with normal hemostasis, patient discharge from the ICU may be delayed for safe removal and subsequent observation. For many practitioners who oppose neuraxial and, in particular, catheter-based techniques in patients with subsequent full heparinization, the risks outweigh the potential benefits.

**Potential benefits of neuraxial techniques**

Some of the benefits have already been mentioned in the previous section and many are related to superior pain control and consequently reduction in systemically administered analgesic and sedation requirements. Several studies in patients undergoing CHS compared an IV pain medication regimen with a combined IV and neuraxial technique. Hammer et al. [114] performed a prospective, randomized trial in children undergoing CHS, assessing the effects of adding single-shot subarachnoid tetracaine and morphine to an inhalational/remifentanil anesthetic. The analgesic effects of subarachnoid morphine were long-lasting and 8- and 24-hour pain scores and fentanyl requirements in the postoperative period were significantly lower in the spinal group compared with IV fentanyl only. Similarly, Rojas-Perez et al. also found reduced fentanyl requirements in children undergoing cardiac surgery with caudal morphine and bupivacaine [109]. Suominen et al. [144] examined the effects of a single-shot subarachnoid morphine (20μg/kg) bolus in children undergoing CHS. In this prospective, randomized, and observer-blinded study, intrathecal morphine was associated with superior pain control following surgery as evidenced by longer time to first bolus administration and lower total IV morphine requirements. The IV drug-sparing effects were observed for 12 hours after surgery. Interestingly, intrathecal morphine was not significantly associated with earlier extubation and shorter time in the ICU, which is frequently shown with epidural anesthesia. Another prospective study in children undergoing stage 2 and 3 palliation for single-ventricle CHD compared a primarily caudal technique with an IV drug regimen [145]. Both parents and postoperative care team were blinded to the analgesic regimen. The use of caudal morphine significantly delayed the need for postoperative rescue morphine only in stage 3 patients. Surprisingly, overall IV morphine requirements did not differ between the groups. Most studies in adult cardiac surgery confirm superior pain control with neuraxial anesthesia added to a general anesthetic [146–148].

Despite these findings, critics will rightfully say that adequate pain control can also be achieved with IV analgesic drug administration. What seems more important than actual pain control, however, is how the IV drug sparing effect translates into other outcome measures. For example, multiple studies report earlier extubation and less time on MV with neuraxial analgesia [109,147,148,149–153], and associated benefits such as reduction in respiratory complications have been discussed in detail earlier in the chapter. Findings of earlier recovery of intestinal function with neuraxial anesthesia[154] may also translate to the CHS setting, particularly if patients are mobilized earlier and enteral feeding can be commenced. Additional information can be gained from the adult literature. A large meta-analysis that included 1,178 patients from 15 randomized trials examining the effects of thoracic epidural anesthesia in coronary bypass surgery found decreased pulmonary complications, dysrhythmias, and time to extubation [155]. While improved postoperative pulmonary function is also reported by several other adult studies [153,157], the largest prospective randomized trial to date was unable to demonstrate a benefit of neuraxial anesthesia in preventing pulmonary complications or mortality [158]. A recent meta-analysis by the same author, however, included 31 randomized controlled trials with a total of 3,047 patients, comparing outcomes in adult patients undergoing cardiac surgery with either general anesthesia alone or in combination with thoracic epidural anesthesia [159]. This analysis confirmed a risk reduction for respiratory complications and supraventricular arrhythmias.

The effect on ICU and hospital LOS is controversial, with some studies suggesting reduced LOS with a neuraxial technique [156], while others did not observe a difference [148,151,152,160–162]. A large prospective observational study in adult cardiac surgery patients compared general anesthesia supplemented with a thoracic epidural
technique with general anesthesia alone. The addition of thoracic epidural anesthesia resulted in shorter time on MV and fewer postoperative complications, such as delirium, pneumonia, acute renal failure, and myocardial dysfunction, resulting in shorter ICU LOS as well as reduced cost [156].

Additional benefits of neuraxial anesthesia include blunting of inflammatory response to surgery and CPB. In children undergoing CHS, plasma norepinephrine and epinephrine concentrations [136] and 24-hour urinary cortisol excretion [163] were reduced with intrathecal drug administration. Additional benefits reported are less inotropic support requirements and greater hemodynamic stability, fewer arrhythmias, and improved ventricular function [166]. Data on biomarkers of myocardial injury in adult cardiac surgery were reduced in some studies [167], while others did not observe any difference when an epidural catheter was used [168]. Lee et al. [169] found that a total spinal with subarachnoid bupivacaine before induction of general anesthesia in adult cardiac surgery patients resulted in less β-receptor dysfunction in response to CPB, lower catecholamine levels, a higher cardiac index, and a lower PVR index in the post-CPB period. In adults undergoing cardiac surgery, thoracic epidural blockade has also been shown to enhance coronary perfusion [170–173]; however, it is unclear if all these findings from the adult literature on neuraxial anesthesia can be transferred to children undergoing CHS.

Overall, the majority of studies in children as well as adults suggest that there are benefits in adding a neuraxial technique to the anesthetic regimen in patients undergoing cardiac surgery. Benefits supported by best evidence include superior pain control, less time on MV, and possibly fewer arrhythmias. With these and many of the additional benefits in mind, adding a neuraxial technique to the anesthetic regimen seems to be suited to facilitate fast-tracking CHS patients.

**Risks and complications of neuraxial techniques**

Many of the typical side-effects of neuraxial anesthetics are not specific to cardiac surgery. Hemodynamic side-effects such as hypotension and bradycardia typically seen with neuraxially administered local anesthetics in adults are less pronounced in children [174]. Nausea and vomiting occur less frequently and prevention with commonly used drugs such as serotonin 5-HT3 receptor antagonists or a combination of drugs should be considered if very early extubation is planned [175]. Pruritus occurs in a very high percentage of cases, especially following intrathecal opioid administration. Diphenhydramine is a popular first-line choice for treatment. Its effectiveness for pruritus related to neuraxial opioids is limited, however, and small amounts of naloxone [176] or even mild sedation, e.g., with dexmedetomidine [177], or small amounts of propofol [178] are often more effective choices. Mild respiratory depression is common with neuraxial opioid administration. Mild hypercarbia and respiratory acidoses are frequently seen, especially following early extubation; however, this is usually very well tolerated and rarely requires reintubation. Close observation in a monitored unit is recommended for 24 hours after neuraxial morphine administration, which is rarely a problem in children undergoing CHS. Continuous positive airway pressure (CPAP) can be applied nasally or via facemask to support respiratory efforts. Urinary retention is not a problem in this patient population as almost all cardiac patients, including children, have a urethral catheter inserted. Ideally, all neuraxially administered drugs should be labeled for neuraxial use by the manufacturer. Particular attention should be paid to avoid drugs with added preservatives, some of which have been found to be neurotoxic when injected via the neuraxial route [179]. As few drugs are approved specifically for neuraxial administration, however, off-label use is common.

The most feared complication of a neuraxial regional anesthetic technique is an epidural hematoma. This is of particular concern in patients eventually undergoing full heparinization for CPB. Unlike in adults, the pre-operative insertion of an epidural catheter in an awake child is rarely possible. Typically, neuraxial techniques are performed in the anesthetized child, prohibiting patient feedback during needle and catheter manipulation as well as injection. In order to perform a neuraxial technique safely, common considerations for neuraxial anesthetics must be followed, and careful attention to the most recent guidelines on neuraxial anesthesia in the setting of anticoagulant and antiplatelet agents is of paramount importance [180]. Guidelines are published and regularly updated by the American Society of Regional Anesthesia (ASRA) [181]. Currently, the recommended time interval between neuraxial manipulation and full heparinization is 60 minutes. In practice, heparin is often administered earlier. For example Weiner et al. [182] reviewed the medical records of 714 children who underwent CHS and also had either single-shot caudal or intrathecal morphine as part of their anesthetic regimen (no catheter insertion). There were no cases of symptomatic spinal or epidural hematomas. Further analysis showed that the time interval between full heparinization and neuraxial technique was less than 1 hour in 466 patients. Specifically, 299 patients were heparinized less than 45 minutes following neuraxial technique, including 270 caudal and 29 spinal morphine administrations; in 86 patients heparin was given less than 30 minutes after the neuraxial technique. While this case series is too small to draw conclusions about the safe timing of single-shot neuraxial anesthesia and consequent heparinization, it provides further support that as long as the coagulation system is intact neuraxial manipulation can be performed safely. To date, there has only been one case of epidural hematoma reported in pediatric patients undergoing CHS. Rosen et al. reported a case of an adolescent who developed an epidural hematoma 2 days after surgery and epidural catheter placement. With the catheter...
in situ, IV heparin was started for prosthetic valve thromboprophylaxis, and alteplase was administered additionally for management of a thrombosed central venous line [183]. More recently, the same group reviewed 750 records of children (52% infants) undergoing CHS who also had an epidural catheter placed as part of their anesthetic regimen and did not find any further neurologic complications [16].

While under-reporting may occur, the actual number of cases performed in clinical practice also far outweighs published case numbers. Given the very low incidence of this serious complication, it would require well-designed prospective studies with thousands of patients for an accurate risk calculation. Additional information can be gained from publications in adult patients undergoing cardiac surgery [184]. Chakravarthy et al. [185] presented an audit of 2,113 cardiac surgery thoracic epidural anesthesia cases over a 13-year period with no permanent neurologic deficits, a 0.9% dural puncture rate, and 0.2% transient neurologic deficits. Jack et al. published their experience of thoracic epidural catheter placement in 2,837 patients undergoing cardiac surgery [186]. No epidural hematoma was seen in this series. Similar results were reported by Royse et al. [187], who reviewed 874 cardiac surgery cases involving epidural anesthesia over a 7-year period with no complications attributable to epidural catheter use. Pastor et al. [188] reported 714 uneventful cases in patients undergoing CABG surgery over a 7-year period. Overall, there are only very few cases of epidural hematomas associated with epidural anesthesia reported in adult cardiac surgery [189–191]. The vast majorities of studies are reassuring and confirm the safety of neuraxial anesthesia in adult cardiac surgery [192–196].

Several attempts have also been made to statistically estimate the actual and presumed risk of an epidural hematoma in patients undergoing cardiac surgery. A widely quoted estimation of the risk of epidural hematoma with thoracic epidural anesthesia in patients undergoing cardiac surgery is 1 in 12,000, with 95% confidence intervals (CI) of 1/2,100 to 1/68,000, and 1 in 1000 with 99% confidence [197]. A recent update of risk assessment in cardiac surgery included source data up to 2012 and found the risk of catheter-related epidural hematoma to 1 in 5,493 (95% CI: 1/970–1/31,114), which is similar to the risk of catheter-related epidural hematoma in the general surgery population (1 in 6,628; 95% CI: 1/1,170–1/37,552) [198]. Intrathecal risks from a different older source of data on regional anesthesia in children over a 1-year period [205]. Data on 31,132 regional anesthetics were collected and analyzed. The overall complication rate was 0.12%; most were minor, and none resulted in permanent neurological damage. In Britain, data on epidural catheter analgesia in children were collected over a 5-year period [206]. A total of 10,633 catheter insertions in children were reported. Serious complications occurred in five children (1/2,000) resulting in permanent damage in one child; low severity events were more frequent (1/189). Insertion of epidural catheters in neonates was associated with a higher risk.

In summary, available data on the safety of neuraxial anesthesia in patients undergoing CHS suggest that these techniques can be performed with minimal risk as long as current guidelines are followed. Additionally, when planning for neuraxial anesthesia, medico-legal concerns should also be considered in some CHS with known inherent risk of spinal cord injury (i.e., coarctation of aorta repair) [207].

### Regional blocks

Regional blocks can be a useful adjunct to an anesthetic and pain regimen in children undergoing CHS. Fewer side-effects and avoiding the risks of systemic heparinization are clear benefits. Various techniques, including paravertebral blocks [208,209], interpleural infusion of local anesthetics [210,211], and subcutaneous wound infiltration techniques [212], have all been described in CHS. Intercostal blocks can be easily performed by the surgeon in the field, and parasternal intercostal blocks can be performed prior to skin closure. Chaudhary et al. conducted a double-blind randomized trial in 30 children undergoing CHS, comparing 0.08 mL/kg/space of 0.5% ropivacaine with 0.9% saline injected in five parasternal spaces on each side before skin closure [213]. They reported no complications, improved pain scores, less postoperative opioid requirement, and shorter time to endotracheal extubation.
Additionally, infusion of local anesthetics via paravertebral catheters has also been reported in children and can be a good alternative to an epidural catheter for management of postoperative pain [214]. El-Morsy et al. [215] performed a prospective randomized study comparing thoracic epidural with paravertebral catheter placement in 60 children (age 1–24 months) undergoing CHS. Analgesia, serum cortisol level, and pulmonary function parameters were comparable; however, failure rate and complications were more frequent in the epidural group. In a review of the literature and meta-analysis of epidural vs. paravertebral catheter insertion in adult patients undergoing thoracotomy, Davies et al. also found fewer side-effects such as nausea, vomiting, and hypotension associated with a paravertebral technique [216]. Even less information is available regarding the risk of developing a hematoma in anticoagulated patients after a paravertebral block. It has therefore been recommended to follow the same guidelines used for neuraxial blockade [217].

**KEY POINTS: NEURAXIAL TECHNIQUES**

- Multimodal pain management strategies include IV, as well as regional or even neuraxial techniques.
- Neuraxial manipulation with subsequent systemic heparinization for CPB is controversial.
- There are increasing data showing that neuraxial techniques can be used safely in CHS.
- The benefits of neuraxial anesthesia beyond superior pain control are increasingly recognized.

**Conclusions**

Fast-tracking patients undergoing CHS has become a viable alternative to a more traditional approach of prolonged postoperative sedation and MV in CHS. Modern anesthetics allow early extubation and adequate pain control without compromising patient safety. In eligible patients, fast-tracking can offer benefits. The overall success of fast-tracking CHS patients requires careful patient selection, recognizing contraindications, and most importantly embracing the fact that this is a multidisciplinary approach involving all specialties involved in CHS patient’s care [218]. Each individual component is equally important for the success of implementing and maintaining fast-tracking in a CHS program.

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A full reference list for this chapter is available at:
http://www.wiley.com/go/andropoulos/congenitalheart

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CHAPTER 21
Anesthesia for Left-to-Right Shunt Lesions

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Introduction

Left-to-right shunt lesions are the most common congenital heart defects, accounting for approximately 50% of all lesions. They are defined by a communication between the systemic and pulmonary circulations that allows shunting of well-oxygenated (systemic) blood to the less oxygenated (pulmonary) circuit. This definition applies whether the associated structures are located on the left or right side anatomically. For instance, a child with a ventricular septal defect (VSD) and L-transposition of the great arteries (ventricular inversion) will shunt blood from the right-sided systemic ventricle to the subpulmonic, lower-pressure, left-sided ventricle. The degree of shunting through a left-to-right shunt lesion may be limited by the size of the defect or the resistance to blood flow on either side. For example, shunting between high-pressure systems like the ventricles through a large VSD is dependent on the ratio of pulmonary vascular resistance (PVR) to systemic vascular resistance (SVR). In contrast, left-to-right shunting through a large atrial septal defect (ASD) occurs primarily during atrial contraction and is dependent on the relative diastolic compliances of the right and left ventricles into which the atria eject.

All left-to-right shunts produce a volume burden on the cardiovascular system, the effects of which vary according to the location of the shunt. Shunting at the level of the great arteries results in increased pulmonary artery blood flow, which increases pulmonary venous return to the left atrium, leading to increased left ventricular end-diastolic volume and left ventricular stroke work by the Frank–Starling mechanism. The left ventricle gradually dilates and hypertrophies, producing increased left ventricular end-diastolic pressure followed by increased left atrial pressure. Shunting at the level of the great arteries...
also produces a decrease in diastolic blood pressure from run-off of blood into the low-pressure pulmonary circuit after closure of the aortic valve. Low diastolic pressures decrease coronary perfusion, potentially creating ischemia from decreased myocardial oxygen delivery in the setting of increased oxygen demand from the hypertrophied ventricle. The final result is pulmonary edema from pulmonary venous congestion and left heart failure. As PVR increases, there is an increased pressure burden on the right ventricle and eventual right heart failure.

Shunting at the atrial or ventricular level, if significant, results in an increased right ventricular volume load, in addition to the hemodynamic effects present with shunting at the great artery level. Prolonged exposure of the pulmonary vasculature to increased flow and pressure results in a fixed increase in PVR. When PVR exceeds the SVR, shunt reversal occurs, resulting in cyanosis and erythrocytosis. Eisenmenger syndrome results when this level of PVR becomes irreversible.

Hemoglobin concentration is another contributing factor to the amount of left-to-right shunting. Elevated blood viscosity, which rises with increasing hemoglobin concentration, increases both PVR and SVR. The net effect is a reduction in left-to-right shunting. The physiologic decline in hemoglobin concentration in the first 3 months of life is thought to have a substantial role in the normal fall of PVR after birth, and may contribute to exacerbation of symptoms related to left-to-right shunting. Figure 21.1 presents a schematic representation of the pathophysiology of the left-to-right shunting lesions.

The normal compensatory mechanisms that maintain systemic cardiac output and myocardial performance

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**Figure 21.1** Pathophysiology of left-to-right shunting lesions. The flow diagram depicts factors that affect left-to-right shunting at the atrial, ventricular, and great artery level and the pathophysiology produced by these shunts. A large shunt will result in left ventricle (LV) failure, right ventricle (RV) failure, and pulmonary edema. Increased pulmonary blood flow and pulmonary artery pressures lead to pulmonary hypertension and eventually Eisenmenger syndrome. These final common outcomes are highlighted in bold lettering. PVR, pulmonary vascular resistance; SVR, systemic vascular resistance; LA, left atrium; BP, blood pressure; RVEDV, right ventricular end-diastolic volume; RVEDP, right ventricular end-diastolic pressure; LVEDP, left ventricular end-diastolic pressure; LVEDV, left ventricular end-diastolic volume; R, right; L, left. See text for detailed discussion.
in the patient with a left-to-right shunt include the Frank–Starling mechanism, the sympathetic nervous system, and hypertrophy of the myocardium. Manifestations of these compensatory mechanisms include sweating and tachycardia. Infants are also often tachypneic from decreased lung compliance associated with increased pulmonary blood flow. Tachypnea impairs feeding, and growth failure develops from both decreased caloric intake and increased caloric utilization. Although significant left-to-right shunts induce biventricular failure, infants rarely manifest peripheral edema or jugular venous distension like adults; the most consistent sign of right-sided failure is hepatomegaly.

Anesthetic management for left-to-right shunt lesions should be individualized to the patient, but certain generalities do exist. Premedication with intravenous (IV) or oral drugs such as midazolam (0.05–0.1 mg/kg IV or 0.75–1.0 mg/kg PO) can be safely administered for the purpose of decreasing anxiety and providing more controlled induction of anesthesia [1]. Standard American Society of Anesthesiologists (ASA) monitors along with the use of invasive arterial and central venous pressure monitoring and careful attention to urine output are recommended for all cases involving cardiopulmonary bypass (CPB). Transesophageal echocardiography (TEE), cerebral oximetry, and cerebral blood flow monitoring are also useful monitoring adjuncts (see Chapters 11 and 12 for a more detailed discussion). Patients with severe, poorly controlled congestive heart failure (CHF) may be intolerant to the myocardial depressant effects of inhalational anesthetics, and for this group of patients, IV anesthesia with fentanyl and midazolam is preferred [2–4]. In most situations, however, inhalation induction with sevoflurane is a viable option when IV access is not initially available.

Additional anesthetic issues include avoidance of air bubbles in IV lines to prevent paradoxical emboli. The anesthesiologist must be cognizant of the pulmonary vasodilatory effect of oxygen and hypocarbia and manipulate ventilation in order to balance the PVR and SVR. Such measures generally include minimizing the FiO₂ and avoiding hyperventilation (maintaining PaCO₂ between 40 and 50 mmHg).

**Patent ductus arteriosus**

**Incidence, anatomy, and natural history**

Isolated persistent patent ductus arteriosus (PDA) occurs in approximately 1 in 2,500 to 1 in 5,000 live births. The incidence is higher for premature births and PDA is two to three times more common in females than in males [5–8]. PDA is also found as part of other complex congenital heart defects and is usually the source of pulmonary or systemic blood flow in patients with a functional single ventricle before palliative repair.

The ductus arteriosus is a vascular communication between the descending aorta and the pulmonary artery. Embryologically, it arises from the distal portion of one of the sixth paired aortic arches [5]. It most commonly originates from the aorta, just distal to the left subclavian artery, and attaches to the left pulmonary artery (Figure 21.2) [6].

The ductus arteriosus is an essential component in normal fetal circulation; it becomes functionally closed within 10–15 hours after birth and permanently closes by thrombosis, intimal proliferation, and fibrosis in the first 2–3 weeks. Functional closure is initiated by several mechanisms, including aeration of the lungs, removal of prostaglandins produced in the placenta, increased arterial PO₂, and release of vasoactive substances (bradykinin, thromboxanes, and endogenous catecholamines) [5,7–9].

The consequences of a PDA left untreated depend on many factors. A small PDA may be hemodynamically insignificant and unrecognized. The larger the PDA and left-to-right shunt, the more likely the progression to CHF, pulmonary hypertension, and, if chronic and/or extreme, reversal of the shunt. In premature infants, PDA may result in increased morbidity from associated respiratory distress syndrome, necrotizing enterocolitis, and intracranial hemorrhage.

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Figure 21.2 Patent ductus arteriosus. Ao, aorta; PA, pulmonary artery; RV, right ventricle; LV, left ventricle. (By Patrick J. Lynch, medical illustrator http://creativecommons.org/licenses/by/2.5, via Wikimedia Commons.)
Pathophysiology
The degree of left-to-right shunting depends on several factors, including the size of the PDA and the ratio of PVR and SVR. Ductal dimensions of importance include diameter and length. Larger diameters and shorter lengths produce less resistance, with the potential to allow greater flow. In patients with large PDAs, the diastolic runoff into the pulmonary artery results in lowered aortic diastolic pressure, which may increase the risk of myocardial ischemia, especially in the presence of anemia or lowered SVR.

Surgical and transcatheter approaches and outcomes
In premature newborns, initial management of a PDA is typically pharmacological closure using cyclo-oxygenase inhibitors such as ibuprofen or indomethacin [10]. Surgical treatment is usually reserved for patients who fail medical therapy. Surgical options include posterolateral thoracotomy with ligation or division of the PDA [11,12] (Figure 21.3), video-assisted thoracoscopic surgery (VATS), and robotically assisted total endoscopic closure [13]. These approaches have mortality approaching 0% and minimum morbidity; however, mortality rates in premature neonates are slightly higher [7]. Complications of surgical treatment include bleeding, chylothorax, vocal cord paralysis (injury to recurrent laryngeal nerve), pneumothorax, atelectasis, recurrence of patency, and inadvertent ligation of the pulmonary artery or descending aorta [7].

Video-assisted thoracoscopic surgery is increasingly popular due to decreased pain, decreased hospital cost (secondary to decreased hospital stay), and avoidance of post-thoracotomy syndrome (rib fusion, chest wall deformities, scoliosis, and compromise of pulmonary function). Disadvantages of VATS include intraoperative oxygen desaturation and hypercarbia, as well as higher morbidity during the surgical learning curve [14–16]. Use of robotic assistance achieves similar outcomes but with longer surgical times because of increased complexity [13,17].

Non-surgical catheter techniques for PDA closure include Gianturco coils, the Gianturco–Grifka vascular occlusion device (both Cook Medical, Inc., Bloomington, IN, USA), and the Amplatzer duct occluder (St. Jude Medical, St. Paul, MN, USA) [18–20]. These methods are considered safe, efficacious, and cost-effective when compared with surgical closure. Risks of transcatheter approaches include arrhythmias, embolization of the device, and incomplete closure. In addition, there are size limitations in small infants, although newer devices may allow for transcatheter closure in patients less than 5 kg with favorable anatomy [18–23].

Anesthetic considerations
The anesthetic management for PDA ligation depends on factors such as the patient’s clinical condition, prematurity, coexisting disease, body weight, and surgical technique. Large volume venous access (which may be a 22- or 24-gauge IV in a premature infant) and forced air-warming devices are recommended. Pulse oximetry of both upper and lower extremities will assist in detecting inadvertent ligation of the descending aorta. For patients with coexisting disease, intra-arterial pressure monitoring provides a method of assessing arterial blood gases, electrolytes, hematocrit, and acid–base status. Whether by cuff or arterial line, blood pressure should be monitored in both an upper and lower extremity and observed carefully before and after ductal occlusion. Proper ductal occlusion will typically be accompanied by an increase in diastolic blood pressure consistent with elimination of pulmonary runoff. Significantly decreased or absent blood pressure in the lower extremity indicates aortic rather than ductal occlusion. A gradient between the systolic pressure in the upper and lower extremities indicates creation of an aortic coarctation.
Although inhaled anesthetics can be safely used for many patients undergoing PDA ligation, neonates are prone to hemodynamic instability with exposure to inhaled anesthetics and benefit from an IV anesthetic technique using opioids, such as fentanyl, and possibly a benzodiazepine along with muscle relaxation.

Neonatal PDA ligation is often performed in the newborn intensive care unit (ICU) to avoid the additional risks of transport, need for ventilator changes, and hypothermic exposure. High spinal anesthesia, and caudal and thoracic epidural techniques have all been described as safe and producing faster recovery [24,25].

Lung isolation improves surgical exposure, especially for VATS surgical techniques, but may require ventilation with 100% inspired oxygen to maintain acceptable oxygenation. Prior to lung isolation, FiO₂ should be minimized and hypocarbia avoided in order to maintain pulmonary vascular tone and limit the degree of left-to-right shunting. Lung isolation is usually unnecessary for small infants; gentle retraction and packing during open thoracotomy, or gentle CO₂ insufflation and retraction during VATS are generally sufficient.

Infants having thoracotomy or VATS often require postoperative mechanical ventilation, especially if they are premature. Older patients or patients undergoing transcatheter closure are often extubated at the conclusion of the case [16–23].

### Key Points: Patent Ductus Arteriosus

- PDA is a relatively common congenital heart defect and is associated with prematurity.
- Pathophysiology depends on the degree of shunting, which is greatest with a short ductus of large diameter.
- Surgical closure may involve an open, thoracoscopic, or transcatheter technique.
- Choice of anesthetic is unlimited in older, less symptomatic patients but is often restricted to opioid technique in premature infants.
- Monitoring perfusion above and below the ductus is critical in recognizing inadvertent ligation of the aorta.
- Immediate postoperative extubation is an option for healthy patients and/or transcatheter techniques, but postoperative mechanical ventilation is required for most neonates and infants.

### Aortopulmonary window

#### Incidence, anatomy, and natural history

Aortopulmonary window (APW), also known as aortopulmonary (or aorticopulmonary) fistula, fenestration, or septal defect, is a rare anomaly comprising approximately 0.1–0.6% of all congenital heart defects [26,27]. Fifty to eighty percent of patients with APW have associated defects, including PDA (72%), right pulmonary artery from aorta (32%), anomalous origin of a coronary artery from the pulmonary artery (23%), VSD (20%), agenesis of the ductus arteriosus (20%), and other lesions [26,28]. Embryologically, APW is thought to originate from non-fusion or malalignment of the aortopulmonary and truncal septi, or complete absence of the aortopulmonary septum [26,29].

The basic anatomical defect in APW consists of a communication between the aorta and the pulmonary artery. Type I APW is a proximal defect located just above the sinus of Valsalva, a few millimeters above the semilunar valve. Type II is a distal APW located in the uppermost portion of the ascending aorta. Type III is a total defect involving the majority of the ascending aorta. Type IV or intermediate defects, which are neither proximal nor distal, are also designated in this system; these defects are noted for being conducive to device closure because of adequate superior and inferior rims (Figure 21.4) [30].

Uncorrected APW results in a reported 40% mortality in the first year of life, with a substantial proportion of survivors succumbing to CHF later in childhood [29].

#### Pathophysiology

The pressure gradient between the aorta and pulmonary artery will produce significant left-to-right shunting, depending on the size of the defect and the relative resistances of the pulmonary and systemic vascular beds. A defect such as an APW is considered “restrictive” when it is small enough that there is a size-related flow limitation across the defect indicated by a significant pressure gradient from one side to the other. Flow across a “non-restrictive” APW is not limited by size; any pressure gradient across the defect is related only to the relative resistances of the pulmonary and systemic vascular beds. Coexisting cardiac anomalies may alter the pathophysiology. Pulmonary hypertension can develop as early as 12 days of age [31].

#### Surgical and transcatheter approaches and outcomes

A variety of techniques have been described for repair of APW, including ligation and/or division with or without CPB, transaortic patch closure, complete separation, reconstruction of both the aorta and pulmonary artery, and transcatheter closure [30,32–34]. The repair is usually performed via median sternotomy with the use of CPB. Surgical repair of the aortic defect can be accomplished using a pulmonary artery flap with subsequent repair of the pulmonary artery with pericardial patch [35,36]. A Gore-Tex cardiovascular patch can also be used to close the defect [30] (Figure 21.5). Care must be taken to explore and repair associated anomalies of the pulmonary and coronary arteries, and to repair coexisting cardiac abnormalities. Deep hypothermia and circulatory arrest...
may be required for repair of a large APW involving the proximal ascending aorta in neonates.

Actuarial survival after repair of APW is approximately 90% at 1, 5, and 10 years [26]. Transcatheter closure of APW has been reported utilizing the Rashkind double umbrella as well as the Amplatzer occlusion device [33,34,37]. Although transcatheter closure has generally been reserved for patients with restrictive defects, device closure has been reported in selected non-restrictive defects as well [38].
Figure 21.5 Patch closure of a type III aortopulmonary window total defect. Aortic cross-clamp and cardiopulmonary bypass cannulas not shown. (Source: Tkebuchava et al. [28]. Reproduced with permission of Elsevier.)

Anesthetic considerations
The anesthetic management of APW is similar to that of truncus arteriosus. Younger patients may have considerable diastolic run-off from low PVR. Prior to CPB, efforts should focus on maintaining pulmonary vascular tone. This can be accomplished by lowering the minute ventilation and restricting the \( \text{FiO}_2 \) to maintain a moderate hypercarbic respiratory acidosis and an oxygen saturation level of 80–85%. In these cases, surgical snaring of the pulmonary artery prior to bypass may also be helpful.

By contrast, patients undergoing later repair are likely to present with elevated PVR, and anesthetic management should include avoiding further increases in PVR.

Regardless of PVR at presentation, all patients with APW are at risk of developing perioperative pulmonary hypertension. The administration of inhaled nitric oxide as well as other maneuvers described earlier may be necessary to lower PVR. Those patients exhibiting signs of pulmonary hypertension should initially be maintained under deep sedation with or without neuromuscular blockade during the immediate postoperative periods (see Chapter 28).

 KEY POINTS: AORTOPULMONARY WINDOW

- APW is a rare lesion with a pathophysiology and management scheme that vary with the size and location of the defect.

- Surgical and transcatheter approaches have been used; deep hypothermic bypass and circulatory arrest may be required.
- High pulmonary blood flow and diastolic run-off into the pulmonary circulation should be mitigated by maintaining PVR through a lower oxygen saturation and moderate hypercarbia.
- Pulmonary hypertension precautions should be observed in all patients with APW.

Atrial septal defects

Incidence
Atrial septal defects make up approximately 5–10% of all congenital heart defects, with the secundum ASD comprising nearly 80% of all ASDs. Isolated ASDs are more common in females than in males by a factor of 2:1 [7]. A probe-patent foramen ovale is found in approximately 30% of otherwise normal adult hearts [39]. When associated with other congenital heart defects, an ASD may be a life-saving communication allowing mixing of blood between the pulmonary and systemic circulations. Examples include total anomalous pulmonary venous return (TAPVR), tricuspid atresia, and transposition of the great arteries. In such cases, an ASD may be iatrogenically created as a palliative measure, often on an urgent or emergent basis (e.g. balloon atrial septostomy).

Anatomy
The right and left atria are normally divided by the fusion of two septa: the septum primum and the septum secundum (Figure 21.6). The septum primum develops during the fourth week of gestation and the septum secundum during the fifth week [5]. The septum primum originates posteriorly and advances across the atrial midline, but does not completely septate the atria. The opening it leaves by incompletely advancing to the endocardial cushion is the ostium primum. Later, the ostium secundum forms in the central portion of the septum primum. The septum secundum originates anteriorly and to the right of the septum primum and advances over the ostium primum and secundum. It eventually develops a central opening in its wall called the foramen ovale. The septum primum regresses and becomes the valve of the foramen ovale on the left atrial side [5] [40]. Five different types of ASDs exist: secundum, primum, sinus venosus, patent foramen ovale (PFO), and coronary sinus (Figure 21.7) [41].

Secundum ASD
The secundum ASD is contained within the area bordered by the limbus of the fossa ovalis [42]. It results from an abnormal reabsorption of the septum primum or defective formation or shortening of the septum secundum. Combinations of these abnormalities may contribute to large defects. Secundum ASDs are normally repaired with a patch of autologous pericardium (Figure 21.8A).
Primum ASD
The primum ASD results from abnormalities in formation of the septum primum. It is frequently associated with atrioventricular canal (AVC) defects, especially partial atrioventricular canals (PAVCs) that include a cleft in the anterior leaflet of the left atrioventricular valve. AVC defects are due to abnormalities in fusion of the endocardial cushions. Primum ASDs are also repaired with a patch; repair of the cleft in the left atrioventricular valve is also done if present (Figure 21.8B).

Sinus venosus ASD
Sinus venosus defects result from abnormal development of the septum secundum or the sinus venosus (the primitive venous collecting chamber). The most common type is located near the superior vena cava (SVC) orifice and is associated with partial anomalous pulmonary venous return (PAPVR) involving the right upper and middle pulmonary veins. Defects near the orifice of the inferior vena cava (IVC) also exist and may involve PAPVR of the right lower pulmonary vein [7].

Patent foramen ovale
Patent foramen ovale results from failure of fusion of the septum primum to the limbus of the septum secundum. Patency of the foramen ovale is normal during fetal life and allows right-to-left shunting of blood in order to bypass the lungs in fetal circulation. Following birth, PVR decreases and SVR increases. Subsequent higher pressure in the left atrium causes the septum primum to close over the foramen ovale, but it may not completely fuse to the septum secundum.
Coronary sinus ASD

Coronary sinus ASD, also called an unroofed coronary sinus, results from an absence in the wall between the coronary sinus and the left atrium. This allows blood from the left atrium to drain into the right atrium via the coronary sinus. Persistent left SVC is also associated with this defect [42].

Natural history

Isolated ASDs are usually asymptomatic during infancy and childhood, despite the increased volume load on the right ventricle. CHF usually occurs after the second or third decade of life due to chronic right ventricular volume overload. Pulmonary hypertension can occur in up to 13% of unoperated patients younger than 10 years of age; however, progression to Eisenmenger syndrome is unusual [7]. Risk of arrhythmia is increased with increasing shunt volume and atrial dilation. Patients with a pulmonary-to-systemic blood flow ratio (Qt/Qs) of 2:1 or less have an 11% incidence of atrial arrhythmia, compared with 38% in those with Qt/Qs of 3:1 or greater [43]. An ASD is sometimes discovered during a neurological work-up for transient ischemic attacks or strokes from paradoxical emboli [42].

Pathophysiology

The amount of left-to-right shunting at the atrial level is dependent on two factors: the size of the defect and the relative compliance of the right and left ventricles. Shunting occurs primarily during diastole and produces a volume burden on the cardiovascular system that is proportionate to the degree of shunting.

Surgical and transcatheter approaches and outcomes

Surgical repair of an ASD is usually recommended between the ages of 3 and 5 years [44]. Spontaneous closure of small secundum type ASDs occur in up to 87% of infants in the first year of life [7], and controversy exists regarding the closure of small ASDs that are asymptomatic. Conventional surgical treatment involves median sternotomy with the use of CPB to perform a primary repair or patch closure, with surgical mortality approaching 0% [7,45]. Sinus venosus defects are usually repaired using a patch to close the ASD and baffle the anomalous pulmonary veins to the left atrium. The superior vena cava (SVC) may need to be translocated and anastomosed to the right atrial appendage to avoid baffle obstruction (Warden procedure). Many centers now favor partial sternotomy approaches because of the improved cosmetic result with similar morbidity and mortality to complete sternotomy [46–48]. Robotically assisted totally endoscopic ASD repair with remote access perfusion (using femoral cannulation) has been described in adults [49]. With conventional repair, postoperative dysrhythmias are reported in 23% of patients, and as many as 2% of patients may need a pacemaker following surgery [7].

Increased use of transcatheter ASD closure in the cardiac catheterization laboratory has dramatically reduced the number of operative repairs. FDA-approved devices include the Amplatzer septal occluder, the CardioSEAL...
septal occluder (Nitinol Medical Technologies, Inc., Boston, MA, USA), and the Helex septal occluder (W.L. Gore & Associates, Inc., Newark DE, USA) [50]. Non-surgical transcatheter closure of PFO without an occluding device has also been described, using either radio frequency ablation or suture closure [51,52]. Transcatheter ASD closure is usually performed under general anesthesia with the use of TEE to guide placement. However, intracardiac echocardiography using intravascular two-dimensional imaging may eliminate the need for TEE and reduce the need for general anesthesia [53]. Transcatheter closure is safe, associated with decreased hospital stay, lack of a surgical scar, avoidance of CPB, and reduced anesthetic requirements. Limitations to transcatheter closure of ASD include patient size (introducer sheaths may be too large for smaller patients), type of ASD (usually limited to PFO or secundum), and the requirement for an adequate tissue rim to which the device can attach [54]. Occasionally, pre-procedure transthoracic echocardiography does not provide complete information about septal tissue rim size or other requirements for device closure, and backup surgical repair can be arranged during the same anesthetic if the TEE examination reveals contraindications to a transcatheter procedure.

Anesthetic considerations
Patients with an isolated ASD are generally asymptomatic and do not have pulmonary hypertension. Therefore, the induction of anesthesia can be safely accomplished with either inhalation or IV techniques. Whenever possible, patients should have an intraoperative TEE performed prior to incision, because transthoracic echocardiographic studies are sometimes unable to exclude the possibility of PAPVR due to difficulty in visualizing all four pulmonary veins. During surgery, TEE can be helpful in assessing de-airing of the left heart and adequacy of the repair. Most patients have good myocardial function and do not require inotropic support perioperatively. Maintenance of anesthesia typically consists of a combination of inhaled and IV agents. Adjunct regional techniques are favored by some, and may facilitate early extubation [55–58]. Tracheal extubation in the operating room has been shown to decrease patient charges without compromising patient care when compared with extubation in the ICU [59,60]. Whatever technique is chosen, the primary goals for the uncomplicated ASD patient should include preparation for an early extubation either in the operating room or within the first 4 hours postoperatively.

KEY POINTS: ATRIAL SEPTAL DEFECT

- ASDs are a common congenital heart lesion and may be important in maintaining adequate intracardiac mixing in association with other life-threatening heart defects.
- Untreated ASDs may be asymptomatic until CHF, atrial arrhythmias, or stroke from paradoxical emboli occur, generally after the second or third decade of life.
- Anesthesia for isolated ASD closure is generally well tolerated and early extubation is an important goal.
- Transcatheter techniques for ASD closure have dramatically reduced the number of operative repairs.

Ventricular septal defects

Incidence
Ventricular septal defect is the most common congenital heart defect, occurring in 50% of all children with congenital heart disease (CHD) and in 20% as an isolated lesion. Reported incidence ranges from 1.56 to 53.2 per 1,000 live births [61]. VSD is associated with a variety of inherited conditions, including trisomy 13, 18, and 21 as well as VACTERL (vertebral, vascular, anal, cardiac, tracheoesophageal fistula, renal, and limb anomalies) association and CHARGE (coloboma, heart anomaly, choanal atresia, retardation, and genital and ear anomalies) syndrome [62].

Anatomy
Embryologically, the primitive left ventricle is formed from the ventricular portion of the bulbis cordis and the primitive right ventricle is formed from the proximal portion at approximately 23–25 days’ gestation. Disruption of ventricular septation at a given point during primary morphogenesis is responsible for the four different types of VSD: type I, subarterial; type II, perimembranous; type III, inlet; and type IV, muscular (Figure 21.9) [62,63]. Each of these types has various synonyms, making VSD nomenclature somewhat complex. A thorough understanding of the anatomy of the normal ventricular septum is helpful in making sense of the various types and subtypes of VSDs. In this way, VSDs may be understood as those within the muscular portion of the ventricular septum (type IV) and those that exist at its margins (types I–III) near the tricuspid and pulmonary valves.

Type I: subarterial VSD
The subarterial (also called subpulmonary, supracristal, conal, or infundibular) VSD is located just beneath the pulmonary valve, within the outlet septum, above the crista supraventricularis (this defines the inferior margin of the smooth-walled muscular tube of tissue connecting the right ventricle to the pulmonary artery known as the infundibulum or conus arteriosus). As a result of the location of this defect, a Venturi effect may be produced by the jet of blood flowing through the VSD, causing the right or non-coronary aortic cusp of the aortic valve to prolapse toward the defect, producing aortic insufficiency [7]. This type of lesion is more common in the Asian population [64] and comprises approximately 5% of all VSDs.

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Type II: perimembranous VSD
The perimembranous (also called paramembranous or conoventricular) VSD is a communication adjacent to a portion of the membranous septum and the fibrous trigone of the heart, where the aortic, mitral, and tricuspid valves are in fibrous continuity [7]. These infracristal defects (below the crista supraventricularis) are the most common VSD subtype, accounting for approximately 80% of VSDs.

Type III: inlet VSD
Inlet VSDs (also called canal type) are located in the posterior region of the septum beneath the septal leaflet of the tricuspid valve. These defects account for approximately 10% of VSDs.

Type IV: muscular VSD
Muscular VSDs are located anywhere within the muscular portion of the interventricular septum. These defects can be multiple and represent approximately 2–7% of VSDs.

Natural history
Patients presenting with VSD may be asymptomatic or exhibit signs and symptoms of CHF in varying degrees.

Pathophysiology
Isolated VSDs produce left-to-right shunting at the ventricular level, predominantly during systole. In contrast to...
ASDs, in which ventricular dilation is isolated to the right ventricle, the volume load induced by shunting through a VSD affects both ventricles. A VSD may be restrictive or non-restrictive, depending on size. A clear definition of a non-restrictive defect is elusive. Presence of a pressure gradient across the defect is inadequate, because a gradient generally exists even in non-restrictive lesions related to the relative resistances of the pulmonary and systemic vascular beds. Proposed definitions involve the cross-sectional ratio of the defect to aortic orifice, defect size vs. body surface area, or shunt flow velocity [69].

In addition to the pathophysiology associated with left-to-right shunting, VSDs may be associated with secondary structural cardiac anomalies not related to the shunt and resultant volume loading. An example is the aortic valve prolapse often associated with VSDs near the aortic valve, resulting in aortic insufficiency. Another is the phenomenon of a “double-chambered right ventricle,” which occurs with some frequency in the setting of a VSD. In this lesion, mid-cavity obstruction by hypertrophied muscle bands creates a high-pressure proximal chamber and a low-pressure distal chamber within the right ventricle. These lesions are also often associated with discrete subaortic stenosis [69].

**Surgical and transcatheter approaches and outcomes**

Surgical repair of VSD is usually by patch closure and occasionally by primary closure using CPB via median sternotomy. Perimembranous and inlet VSDs are most commonly repaired via a right atriotomy, which may require detachment of the septal leaflet of the tricuspid valve for exposure [41](Figure 21.10). Subarterial VSDs are most commonly repaired via the transpulmonary approach. Midmuscular VSDs are most commonly repaired via right atriotomy, and anterior or apical muscular VSD may be approached using right ventriculotomy. However, the use of a right ventriculotomy carries the risks of conduction disturbances and ventricular dysfunction later in life. Symptomatic patients with lesions that are not approachable via right atriotomy may be treated with pulmonary artery banding until the patient is larger, allowing transatrial repair. Pulmonary artery banding is also utilized for multiple muscular VSDs and in patients who are high-risk candidates for CPB. Partial median sternotomies as well as small right anterolateral thoracotomies are advocated by some because of improved cosmetic results [70,71]. Video-assisted cardioscopy (VAC) is used in some centers to improve visualization of small intracardiac structures in limited spaces during open-heart surgery for congenital heart repairs. VAC has been successfully utilized for a variety of intracardiac repairs, including ASD, VSD, tetralogy of Fallot, double outlet right ventricle (DORV), AVC, and others [72–74].

Timing for surgical repair varies depending on age at presentation and severity of signs and symptoms. Patients younger than 6 months of age are repaired if they manifest uncontrollable CHF and failure to thrive. Patients between 6 and 24 months of age undergo repair to treat CHF symptoms or pulmonary hypertension. Patients older than 24 months undergo repair if the Qp:Qs is greater than 2:1. Among patients with subarterial VSD, the presence of aortic insufficiency is an indication for surgical repair to prevent further progression of the valvular insufficiency [75,76]. A defect size of greater than 5 mm is repaired to avoid progression to aortic cusp prolapse and aortic insufficiency, and defects less than 5 mm can be managed conservatively [64]. However, even small, otherwise asymptomatic VSDs are usually repaired because of the small risk of infective endocarditis.

Mortality for uncomplicated VSD in older patients is less than 1–2% [77]. Mortality for VSD repair in infants during the first year of life is less than 5% [78].

Transcatheter closure of VSDs has been performed successfully for more than 25 years [79–84]. In the USA, the CardioSEAL septal occluder and its replacement, the
Anesthetic considerations

Anesthetic management for the patient with VSD is similar to that of ASD. Pulmonary hypertension may develop early, especially in patients with trisomy 21, and preoperative chest radiograph revealing decreased pulmonary vascular markings is indicative of pulmonary hypertension [86–93]. Such patients may respond to the use of inhaled nitric oxide prior to termination of CPB and/or in the postoperative period. Right heart failure with decreased cardiac output may result if pulmonary hypertension is not controlled, and may require the use of dopamine, milrinone, dobutamine, or isoproterenol.

Conduction disturbances may be transient or permanent. Atrioventricular block, formerly reported to occur in up to 10% of patients post-VSD repair [7], is now a rare complication occurring in less than 1% of patients after VSD closure [7]. If heart block develops, treatment with atrioventricular synchronous pacing using temporary pacing wires is indicated. Junctional ectopic tachycardia is sometimes observed in patients younger than 1 year after surgery for lesions that involve VSD repair, most commonly after tetralogy of Fallot correction. Treatment includes cooling to 35°C, increasing anesthetic depth, paralysis, procainamide, esmolol, or amiodarone [7].

Intraoperative use of TEE will allow recognition of residual VSDs and intracardiac air, as well as providing an assessment of ventricular volume and function. Small muscular VSDs often become apparent after closure of larger VSDs. Frequently these smaller defects, especially if near the apex, may not be amenable to surgical repair or worth the risk of returning to CPB.

Patients with uncomplicated VSDs are good candidates for extubation in the operating room or early after arrival in the ICU.

Key Points: Ventricular Septal Defect

- VSDs are the most common congenital heart defects
- Both ventricles are affected by left-to-right shunting through a VSD
- Pulmonary vascular tone should be maintained in those patients with pulmonary overcirculation prior to repair
- Be prepared to treat arrhythmias, including heart block and junctional ectopic tachycardia, especially after repair
- Patients with uncomplicated VSDs should be considered for early extubation.

Atrioventricular canal

Incidences

Four to five percent of CHD involves defects of the atrioventricular septum, and AVC defects occur in 0.19 in 1,000 live births [93,94]. AVC is associated with multiple syndromes and occurs in approximately 20% of persons with trisomy 21. It accounts for 15% of congenital heart defects in patients with Noonan syndrome and nearly 50% in those with Ellis–van Creveld syndrome [95].

Anatomy

Atrioventricular canal defect results from failure of the endocardial cushions to fuse during the fifth week of fetal development [5]. AVC consists of three basic defects: an ostium primum defect resulting in an interatrial communication; abnormal atrioventricular valves; and an inlet VSD resulting in an interventricular communication. There are three types of AVC: partial, transitional, and complete [96].

Partial AVC

The PAVC defect consists of an ostium primum ASD and a cleft in the anterior leaflet of the mitral valve, usually resulting in some degree of insufficiency [90]. The tricuspid valve is often abnormal as well, and no VSD or other interventricular communication exists.

Transitional AVC

The transitional (also called intermediate) AVC (TAVC) defect consists of an ostium primum ASD, abnormal atrioventricular valves that form two separate orifices, and a VSD, often restrictive, just below the atrioventricular valves [96]. Like the PAVC defect, the left atrioventricular valve is usually associated with a cleft and has some degree of insufficiency.

Complete AVC

The complete AVC (CAVC) defect consists of an ostium primum ASD and a non-restrictive VSD just below a
common atrioventricular valve that bridges both the right and left sides of the heart to create a single valve orifice [90]. The left atrioventricular portion of the valve usually contains a cleft that is insufficient. Three classifications of CAVC defects exist based on the chordal attachments of the anterior bridging leaflet of the common atrioventricular valve and these are commonly referred to as Rastelli types A, B, and C [96,97] (Figure 21.11).

In Rastelli type A CAVC, which is the most common type, the anterior bridging leaflet is divided at the septum into right and left components and attached to the crest of the ventricular septum by thin chordae tendinae. Rastelli type B CAVC is rare and characterized by anomalous papillary muscle attachment from the right side of the ventricular septum to the left side of the anterior bridging leaflet. Rastelli type C CAVC is defined by an anterior leaflet that lacks any ventricular septal attachments and “floats” above the septum [96]. The Rastelli type C defect may be associated with other major cardiac or extracardiac anomalies such as tetralogy of Fallot or trisomy 21 [42].

Other variants of AVC also exist, including right or left ventricular dominant types in which the common atrioventricular valve opens predominantly into one of the ventricles ("unbalanced" AVC). If one ventricle is hypoplastic, the physiology produced by such lesions is similar to other single-ventricle lesions (see Chapter 25 for a detailed presentation). Many lesions occur in association with AVC, including PDA, tetralogy of Fallot, coarctation of the aorta, subaortic stenosis, left SVC, and asplenia and polysplenia syndromes [7].

**Natural history**

As with other left-to-right shunts, pulmonary hypertension may develop by 1 year of age and eventually lead to Eisenmenger syndrome [98]. The severity of CHF and symptoms will depend on the degree of left-to-right shunting and the severity of atrioventricular valve regurgitation. Among the forms of AVC, PAVC is the least symptomatic, CAVC the most, and TAVC intermediate. Patients with untreated PAVC may do well through childhood, but have an increased likelihood of developing CHF in adulthood, especially as atrial dysrhythmias develop [42]. The presence of moderate to severe atrioventricular valve regurgitation leads to earlier development of CHF and higher morbidity and mortality if untreated. Those patients with PAVC presenting with CHF in the first year of life should be suspected of having additional lesions, most commonly left-sided obstructive lesions [99]. Patients with CAVC develop CHF, failure to thrive, and frequent respiratory infections in the first year of life. During this same interval, 12% of these children will develop irreversible pulmonary hypertension. A chest radiograph demonstrating black lung fields, indicating decreased pulmonary blood flow, is an ominous sign [89]. Those with trisomy 21 develop pulmonary hypertension earlier and with increased severity compared with other children; however, this has not manifest as a risk factor in surgical repair or long-term outcome [92,100–102].

**Pathophysiology**

A left-to-right shunt may occur at the atrial, ventricular, and atrioventricular valvular levels, depending on the type of AVC present. This shunting, in addition to atrioventricular valve regurgitation, results in volume overload of both the atria and ventricles. Volume overload soon develops into CHF and may result in pulmonary hypertension as the ratio of pulmonary to systemic blood flow increases.

**Surgical approaches and outcomes**

Surgical repair of PAVC is usually performed at age 2–5 years unless there are signs of CHF or other lesions that necessitate earlier repair. Patients with TAVC may be relatively asymptomatic and may tolerate surgical repair at an older age.

Primary complete surgical repair for patients with CAVC is performed between 1 and 6 months of age.
because it is safe, controls CHF, prevents the development of fixed pulmonary hypertension, and reduces annular dilation (a cause of atrioventricular valvular regurgitation) [99,103,104].

Surgical techniques vary, but generally consist of a right atriotomy with patch closure of the ASD, closure of cleft in the anterior leaflet of the left atrioventricular valve, and closure of the VSD with a patch or, in the case of the TAVC, pledgeted sutures [7,42,103]. A one- or two-patch technique can be used. The one-patch technique consists of a single patch closure of both the ASD and VSD (Figure 21.12) [105]. Pulmonary artery banding is reserved for cases of severe respiratory illness, sepsis, or anatomy not suitable for biventricular repair. Presence of associated cardiac anomalies, such as tetralogy of Fallot, DORV, left-sided obstructive lesions, and unbalanced AVC (with a hypoplastic ventricle), further complicate the repair and result in higher mortality, especially in those patients with a hypoplastic ventricle [106,107].

Mortality for repair of the PAVC is less than 5%, and the mortality for complete repair of CAVC is between 2.5 and 10.5% [7,104,108–110]. Pulmonary artery banding is associated with mortality near 5% [7,42]. The presence of preoperative pulmonary hypertension and increasing size of the VSD are associated with higher morbidity and mortality among patients undergoing complete repair of CAVC [42,108].

Anesthetic considerations
Anesthetic management of the AVC defects depends primarily on the degree of left-to-right shunting, and the presence and severity of pulmonary vascular hypertension. As with other septal defects, balancing the ratio of PVR to SVR and thereby limiting the amount of pulmonary overcirculation is paramount to successful management, and is usually accomplished by manipulations in FiO₂ and ventilation (see earlier). TEE is very helpful in detecting residual intracardiac shunts, assessing atrioventricular valvular function, and determining ventricular function and volume following repair.

Surgical placement of left atrial and pulmonary arterial pressure lines may be used to guide management of inotropes, use of nitric oxide, and volume replacement. Persistent elevation and acute increases in pulmonary arterial pressure contribute to right heart failure and increased mortality [7,108]. Pulmonary hypertension commonly develops in these patients and is treated with hyperventilation, 100% oxygen, systemic alkalinization, opioids, and nitric oxide. Increasing the pH is more effective than lowering the PaCO₂ in controlling pulmonary pressures and may be accomplished by the administration of sodium bicarbonate [111]. Sildenafil has also been effective in this setting [112].

Most patients require inotropic support upon weaning from CPB, and those with residual atrioventricular valve regurgitation and/or VSD benefit from use of milrinone or other afterload reduction. Hypotensive patients who have elevated left atrial pressures should be evaluated for the presence of severe residual left atrioventricular valve regurgitation or stenosis, residual VSD, left ventricular outflow tract obstruction, or left ventricular dysfunction [7]. Intraoperative TEE is essential for initial diagnosis of these conditions, and re-initiation of CPB and repair may be necessary.

Complete AVC repair is associated with conduction abnormalities, especially atrioventricular and sinoatrial nodal dysfunction resulting in complete heart block. In this situation, atrioventricular sequential pacing is necessary to minimize atrioventricular valve regurgitation and improve cardiac output [7].

**KEY POINTS: ATRIOVENTRICULAR CANAL**
- AVC is associated with trisomy 21, Noonan syndrome, and Ellis–van Creveld syndrome.
- AVC may be partial, transitional, or complete.
- Measures to maintain pulmonary vascular tone are necessary to avoid pulmonary overcirculation prior to repair.
- Following bypass, pulmonary hypertension is common and therapy may include nitric oxide, hyperventilation, 100% oxygen, systemic alkalinization, deep sedation, and neuromuscular blockade.
- Inotropic support is often needed post-bypass.
- Residual defects and cardiac function are evaluated by TEE post-repair.
- Dysrhythmias, including complete heart block, are common and temporary pacing may be required.

**Double outlet right ventricle**

**Incidence**
Double outlet right ventricle comprises approximately 1–1.5% of all patients with CHD with an incidence estimated at 1 per 10,000 live births [113]. Although DORV can occur with an intact ventricular septum, this is extremely rare [114]; almost all patients with DORV also have a VSD.

**Anatomy**
Double outlet right ventricle is a type of ventriculoarterial connection in which both great vessels arise either entirely or predominantly from the right ventricle. This definition is intended to simplify what is in fact a complex spectrum of defects, ranging from morphology that mimics tetralogy of Fallot to that which resembles transposition of the great vessels. Embryologically, DORV is a bulboventricular malformation that results from failure of proper alignment of the conotruncus with the ventricular septum [113].

Characterization of the anatomy of DORV is crucial in understanding the physiologic consequences, as well as determining the surgical approach for palliation or correction. Complete characterization of the anatomy will
Figure 21.12 One-patch repair of a complete atrioventricular canal defect. (A) The defect is exposed. (B) The anterior and posterior common valve leaflets are divided to separate the mitral and tricuspid sections. (C) The ventricular septal defect is closed using the inferior portion of the patch. (D) The valve leaflets are anchored to the mid-portion of the patch using pledgets for added support. (E) The mitral valve is rendered bicuspid by closure of the anterior and posterior common leaflets on the mitral side, which had been natively separate, to create a functional mitral valve cleft after being anchored to the patch. (F) The superior portion of the patch is used to close the atrial septal defect. AV, atrioventricular; MV, mitral valve; TV, tricuspid valve (Source: Macris et al. [105]. Reproduced with permission of Texas Heart Institute.)
include: the relationship of the VSD to the great arteries; the relationship of the great arteries with respect to one another; the morphology of the ventricles and their outflow tracts; and the presence of associated anomalies [114]. Four different anatomic types of DORV are defined on the basis of the relationship of the VSD to the great arteries: subaortic VSD, subpulmonary VSD, doubly committed VSD, and non-committed VSD [115,116] (Figure 21.13).

**DORV with subaortic VSD**
These lesions represent approximately 51–56% of DORVs [114,117] and are characterized by a VSD located beneath the aortic valve. The great vessels may be normally related or transposed. When this defect is associated with pulmonary stenosis, the resulting physiology is similar to that of tetralogy of Fallot [113].

**DORV with subpulmonary VSD**
Double outlet right ventricle with subpulmonary VSD represents approximately 30% of DORV [117,118]. Pulmonary stenosis is rare, but subaortic or aortic arch obstructions are common. The VSD is typically non-restrictive. This lesion often occurs in the form of the Taussig–Bing type: with D-malposition of the great arteries in the absence of pulmonary stenosis [113]. The resulting physiology is similar to that of transposition of the great arteries.

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**Figure 21.13** Anatomic subtypes of double outlet right ventricle, as determined by the position of the ventricular septal defect. RA, right atrium; Ao, aorta; PA, pulmonary artery; LA, left atrium; RV, right ventricle; LV, left ventricle. (Source: http://www.rch.org.au. Reproduced with permission of The Royal Children’s Hospital Melbourne.)
DORV with doubly committed VSD
Three to 10% of patients with DORV have a doubly committed VSD [117–119]. The doubly committed VSD results from the hypoplasia of the infundibular septum and variable degrees of override of the VSD by both great arteries [113].

DORV with non-committed VSD
Twelve to 17% of patients with DORV have a non-committed VSD. [114,117], and the VSD is an apical muscular or membranous-inlet type. The VSD is remote from the great arteries and is frequently associated with AVC defects [113].

Natural history and pathophysiology
The natural history and pathophysiology of DORV is dependent on the specific anatomy of the lesion and relative amounts of pulmonary vs. aortic blood flow as well as the degree of mixing of pulmonary and systemic venous blood. Consideration of these variables serves to simplify the pathophysiology of DORV into three basic subtypes: VSD, tetralogy of Fallot, and transposition of the great arteries [120].

Double outlet right ventricle with a doubly committed or subaortic VSD without pulmonary stenosis produces physiology similar to that of a VSD. Because VSDs in this setting are usually non-restrictive, the degree of left-to-right shunting will generally depend on the relative ratio of PVR to SVR.

Double outlet right ventricle associated with pulmonary stenosis resembles the physiology of tetralogy of Fallot with varying degrees of cyanosis, depending on the severity of pulmonic stenosis. These patients have right-to-left shunting across the VSD and may have hypcyanotic spells, erythrocytosis, and failure to thrive. Although there is a fixed component of obstruction, pulmonary blood flow may vary due to alterations in PVR. Pulmonary stenosis is present in approximately 50% of patients with DORV [113].

Double outlet right ventricle with a subpulmonary VSD without pulmonary stenosis usually produces physiology similar to transposition of the great arteries. Streaming of pulmonary venous blood to the pulmonary artery and systemic venous blood toward the aorta results in variable degrees of mixing of oxygenated and deoxygenated blood. Patients can present early with both cyanosis and CHF followed by development of pulmonary vascular occlusive disease if left untreated.

Double outlet right ventricle may be associated with other anomalies that further affect pathophysiology, such as multiple VSDs, AVC defects, PDA, aortic arch obstruction, interrupted aortic arch, subaortic stenosis, hypoplastic ventricle, or mitral valve abnormalities [117–123].

Surgical approaches and outcomes
The surgical approach to DORV varies depending on the type of DORV and the associated anomalies, and the preoperative delineation of anatomy is crucial to determine the operative strategy. However, echocardiography, angiography, and magnetic resonance imaging may still result in incomplete information due to the complexity and anatomic variations of this lesion [122,124]. Often only intraoperative inspection of the heart by the surgeon leads to the definitive operative plan. There are generally four surgical treatment options: (i) palliative procedures such as Blalock–Taussig shunts, coartation repairs, and pulmonary artery banding; (ii) intraventricular repair with a baffle from the left ventricle to the aorta [125] (Figure 21.14); (iii) intraventricular baffle from the left ventricle to the pulmonary artery followed by arterial switch; and (iv) bi-directional cavopulmonary shunt staged to the Fontan procedure (univentricular heart repair) [117–123].

The overall early mortality for the repair of DORV is approximately 9% [117,118,123]. Ten-year survival is 81–86% [117,118]. Significant risk factors for early mortality include congenital mitral valve anomalies, side-by-side great arteries, multiple VSDs, and age at operation <1 month [117–121]. Among patients with DORV and complex anatomy, Fontan palliation may be the procedure of choice as it has been associated with lower early mortality in this group compared with biventricular repair [117].

Anesthetic considerations
Anesthetic management varies greatly depending on the specific type of DORV and associated anomalies. Management of palliative procedures, such as the modified Blalock–Taussig shunt, is reviewed in Chapter 23. Patients with pulmonary stenosis who present with physiology similar to tetralogy of Fallot should be managed to minimize right-to-left shunting (see Chapter 23). Patients with subpulmonary VSD without pulmonary stenosis who have physiology similar to transposition of the great arteries should be managed as such (see Chapter 24). Subaortic and non-committed VSDs without pulmonary stenosis produce physiology similar to that of a VSD and should be managed as described earlier in this chapter. Patients with complex DORV and other associated anomalies that proceed through the single-ventricle staged palliation to the Fontan procedure are reviewed in Chapter 25. In all patients with DORV, regardless of specific anatomy, intracardiac shunting must be balanced with manipulation of PVR and SVR to optimize systemic cardiac output and oxygen delivery.

Arrhythmias are common, especially with repairs involving baffling and enlargement of the VSD. Ventricular tachyarrhythmias and complete heart block can occur in as many as 9% of patients postoperatively and may require permanent pacing [114,117,118]. Frequently, repair of DORV is complex and requires periods of circulatory arrest. Patients may have residual VSDs, valvular insufficiency, outflow tract obstruction, or ventricular dysfunction. Postoperative TEE and left atrial pressure monitoring are helpful in determining the diagnosis and guiding management.
**KEY POINTS: DOUBLE OUTLET RIGHT VENTRICLE**

- The four anatomic subtypes of DORV depend on the location of the VSD: subaortic, subpulmonary, doubly committed, and non-committed.
- DORV with a doubly committed or non-committed VSD is managed as a VSD.
- DORV associated with pulmonary stenosis is managed similarly to tetralogy of Fallot.
- DORV with subpulmonary VSD without pulmonary stenosis is managed similarly to transposition of the great vessels.
- Some patients require single-ventricle staging to a Fontan.
- Postoperative arrhythmias are common.
- Inotropic support is often needed, especially after long bypass intervals.

**Truncus arteriosus**

**Incidence**

Truncus arteriosus is an uncommon congenital heart defect representing less than 3% of all congenital heart defects [7,126–128]. Deletion of chromosome 22q11 is present in approximately 11–35% of patients with truncus arteriosus, and this chromosomal abnormality is associated with DiGeorge and velocardiofacial syndromes. Patients with these syndromes also have non-cardiac anomalies such as aplasia or hypoplasia of the thymus and/or parathyroid glands (T-cell deficiency), hypocalcemia, palatal abnormalities, speech and learning disabilities, neuropsychological disorders, and craniofacial dysmorphism [129–131]. As many as 77% of patients with 22q11 deletion are immunocompromised [131].

**Anatomy**

Truncus arteriosus is defined by the presence of a single great artery arising from the base of the heart that supplies
the coronary, pulmonary, and systemic circulations. Embryologically, this defect results from failure of the truncus arteriosus to divide into the aorta and pulmonary artery.

Truncus arteriosus has historically been classified by two main systems. The first and most widely used classification system was described by Collett and Edwards in 1949 and the second by Van Praagh and Van Praagh in 1965 [132,133]. The Collett and Edwards classification is based on the embryologic arrested development of the pulmonary arteries from the sixth aortic arches and categorized into four different subtypes. For the purpose of this chapter, the Collett and Edwards system will be used (Figure 21.15) [132,134].

**Type I truncus arteriosus**
Type I truncus arteriosus accounts for 70% of truncus arteriosus lesions. It is defined by the origin of the main pulmonary artery from the truncus dividing into left and right pulmonary arteries.

**Type II truncus arteriosus**
Type II truncus arteriosus accounts for 30% and is defined by separate origin of the left and right pulmonary arteries from the posterior surface of the truncus, with the branch pulmonary arteries arising very close to one another.

**Type III truncus arteriosus**
Type III truncus arteriosus is also characterized by separate origin of the left and right pulmonary arteries, but in this case, the arteries arise from the lateral aspects of the truncus and are widely separated. This type accounts for approximately 1% of cases.

**Type IV truncus arteriosus**
Type IV is included for historical purposes, but has been rejected as a true form of truncus arteriosus. It is now defined as a form of pulmonary atresia and VSD and is sometimes called “pseudotruncus.” There is complete absence of the pulmonary arteries in this defect, with bronchial and collateral arteries of the descending aorta providing the blood supply to the lungs.

Truncus arteriosus is most commonly associated with a VSD, but can occur with an intact ventricular septum. The truncal valve may be dysplastic and have an abnormal number of leaflets, varying between two and six [7,133]. Truncal valve insufficiency is estimated to occur in 25–50% of patients; varying degrees of truncal valve stenosis may also occur [133]. Anomalies of the coronary arteries may also exist. Additionally, truncus arteriosus is associated with other cardiac anomalies such as aortic arch obstruction, ASDs (62%), right aortic arch (21–36%), aortic arch interruption (11–19%), PDA (18%), aberrant subclavian
artery (4–10%), absence of one pulmonary artery (10%),
and persistent left SVC (4–9%) [7,126,128].

Natural history
If left untreated, the early CHF and increased pulmonary blood flow associated with truncus arteriosus lead to rapid development of pulmonary vascular occlusive disease in infancy. Patients without surgical treatment have a 74–100% mortality in the first year of life [124–126]. Surgical repair in patients older than 2 years is contraindicated when PVR is greater than 8 Wood units or when Eisenmenger syndrome is present [7,126].

Pathophysiology
Truncus arteriosus, by definition, has a common arterial trunk that provides blood flow to the coronary, pulmonary, and systemic arteries. As PVR falls in the early neonatal period, pulmonary blood flow progressively increases and results in CHF. A variable degree of mixing of the systemic and pulmonary venous blood occurs at the ventricular level through the VSD. The large run-off provided by the pulmonary arteries results in low diastolic pressures, which may be worsened by the presence of truncal valve insufficiency. Low diastolic pressures in the face of increased myocardial work and increased ventricular pressures place the patient at risk of developing myocardial ischemia from coronary steal.

Surgical and transcatheter approaches and outcomes
Definitive surgical repair is usually recommended in the neonatal period, although some centers time surgery on an individual basis, performing repair between 2 and 3 months of age [126–128,135]. Early repair is indicated due to the rapid development of pulmonary hypertension and high mortality rate in patients in the first year of life if left untreated. Palliative surgery involving pulmonary artery banding has largely been abandoned except for those very few patients who are not suitable candidates for definitive repair [128]. Definitive surgical repair involves removal of the pulmonary arteries from the truncal root and closing the resulting defect either primarily or with a patch. The VSD is usually closed with a patch via a transtricusarial or transventricular approach. A right ventricle to pulmonary artery connection is provided by a valved homograft (Figure 21.16) [136]. Direct anastomosis of the pulmonary artery with the right ventricle has been described, but may distort the pulmonary arterial architecture. If high right ventricular pressures are anticipated, a small ASD may be created as a “pop-off” for right-to-left shunting in order to improve cardiac output at the expense of arterial oxygen saturation [7,126,127,134,135]. This ASD creation can be closed at a later date by a transcatheter technique in the cardiac catheterization laboratory. Moderate to severe truncal valve regurgitation is repaired by valvuloplasty, “double-homograft” technique with coronary reimplantation, or mechanical valve implantation [126,137,138]. Valve repair has been successful even in neonates and avoids or delays serial truncal valve replacements [138]. Over time, the right ventricular to pulmonary artery conduit may become stenotic and/or regurgitant. This may necessitate repair or replacement either surgically or via percutaneous techniques (e.g. Melody transcatheter pulmonary valve; Medtronic Inc., Minneapolis, MN, USA) [140]. Much of the long-term pathophysiology after repair of truncus arteriosus is related to truncal valve dysfunction, particularly insufficiency. This contributes to the diminished physical health status of many of these patients in the second decade of life and beyond and may influence anesthetic management for later cardiac or non-cardiac surgery [141]. Early mortality after repair of truncus arteriosus is 5–18%
Anesthetic considerations

Anesthetic management is dependent on the patient’s anatomy and age at presentation. Depending on the severity of CHF, the patient may require preoperative inotropic support, and the induction of anesthesia should be accomplished with drugs that maintain SVR and preserve myocardial function. Ketamine or etomidate, often combined with fentanyl and/or midazolam, may be used to attain this goal safely. If an inhalational induction with sevoflurane is chosen, it should be performed with careful titration and extreme caution. Muscle relaxation may be achieved with any choice of non-depolarizing neuromuscular blocker. Maintenance of anesthesia often includes high-dose opioids, and total fentanyl doses commonly exceed 50 μg/kg. Efforts to balance PVR and SVR to make the ratio of Qp:Qs approach 1:1 are essential. Care must be taken to avoid hyperventilation and excessive oxygenation, which lower PVR and may exacerbate pulmonary overcirculation and decrease diastolic blood pressure. Patients with truncal valve insufficiency combined with excessive pulmonary blood run-off will be particularly susceptible to myocardial ischemia, and it may be necessary for the surgeon to temporarily place a vessel snare around the pulmonary artery to limit pulmonary blood flow and increase diastolic blood pressure in the pre-bypass period. Occasionally this myocardial ischemia is heralded by ventricular fibrillation prior to bypass, and the anesthetic and surgical teams must be alert to this possibility and be prepared to intervene with external or internal defibrillation, open or closed cardiac massage, or emergent institution of bypass. Those patients presenting late in infancy who have developed significant pulmonary hypertension from long-standing pulmonary overcirculation may require increased FiO₂ to maintain oxygen saturations between 80 and 90%. Unless ruled out by a chromosomal evaluation, patients with truncus arteriosus should be assumed to have DiGeorge syndrome and should be given irradiated blood products due to the high incidence of associated T-cell deficiencies. An absent or hypoplastic thymus is often evident upon sternotomy. Upon weaning from CPB, most patients require inotropic support, afterload reduction, ventricular volume assessment, and efforts to minimize pulmonary arterial pressures in order to improve right heart function.

Pulmonary hypertension is commonly present after CPB. These patients have signs of right heart failure with high central venous pressures, desaturation, tachycardia, hypotension, acidosis, and oliguria [7]. Management includes hyperventilation, 100% oxygen, correction of acidosis, and nitric oxide as needed. These patients are usually kept heavily sedated for at least 24 hours postoperatively to minimize early pulmonary hypertensive crises. Signs similar to right ventricular dysfunction may also occur from residual VSDs or truncal valve stenosis or regurgitation. VSD closure or right ventricular incision may produce complete right bundle branch block, complete heart block (3–5%), junctional ectopic tachycardia, atrial tachycardias, or atroventricular block in the postoperative period [76]. After bypass, many patients benefit from calcium infusions because of the hypocalcemia associated with DiGeorge syndrome and citrate binding of ionized calcium from administration of blood products.

KEY POINTS: TRUNCUS ARTERIOSUS

- Truncus arteriosus is associated with DiGeorge and velocardiofacial syndromes.
- Subtypes are defined by the relationship of the pulmonary arteries to the truncus.
- Presence of DiGeorge may necessitate calcium infusions and irradiated blood products.
- Pulmonary overcirculation requires maintenance of PVR pre-bypass and pulmonary hypertension precautions post-bypass.
- Myocardial ischemia may occur due to coronary steal as PVR decreases in the first weeks of life.
- Inotropic support is often necessary perioperatively.

Partial and total anomalous pulmonary venous return

Incidence

Both PAPVR and TAPVR are rare cardiac lesions. As PAPVR is often asymptomatic, its true incidence is unclear, but it has been reported as an incidental finding on autopsy in approximately 0.6% of the general population [142]. TAPVR represents less than 5% of congenital heart lesions [143–145].

Both PAPVR and TAPVR can be associated with other cardiac lesions. PAPVR is most commonly associated with sinus venous type ASDs. Congenital mitral stenosis, DORV, VSD, tetralogy of Fallot, coarctation of the aorta, and PDA have all been described with PAPVR [144]. Nearly 33% of patients with TAPVR have other cardiac anomalies, such as CAVC, hypoplastic left heart syndrome or other single-ventricle lesions, PDA, and transposition of the great arteries. Abnormalities of the atrial and visceral situs with the heterotaxy syndrome, asplenia, and polysplenia are also common among patients with TAPVR [144]. Scimitar syndrome consists of either partial or complete anomalous drainage of the right pulmonary veins to the IVC, dextrocardia, and hypoplasia of the right lung. In these patients, the descending vertical vein resembles a scimitar, or Turkish sword, on a frontal chest radiograph [144].
**Anatomy**

Partial anomalous pulmonary venous return is an anomaly in which some, but not all, of the pulmonary veins connect to the right atrium or to one or more of its venous tributaries. In TAPVR, all of the pulmonary veins connect anomalously to the right atrium. Although these lesions are sometimes referred to as anomalous pulmonary venous connections, use of the term return recognizes the fact that the pulmonary veins may be connected normally to the left atrium, but have an ASD anatomically configured to cause abnormal return to the right atrium [142]. In either case, the pathophysiology is that of a left-to-right shunt.

The stage in embryologic development during which errors occur determines the various anatomic subtypes of abnormal pulmonary venous return. At 27–30 days’ gestation, the pulmonary veins are derived from the splanchnic plexus that communicates with the cardinal and umbilicovitelline system of veins. Anomalous drainage to the left common cardinal system results in pulmonary venous connections to the coronary sinus or left innominate vein. Drainage to the right common cardinal system results in pulmonary venous connections to the SVC and/or the IVC. Early atresia of the common cardinal veins that communicates with the cardinal and umbilicovitelline system of veins. Anomalous drainage to the right common cardinal system results in pulmonary venous connections to the right atrium, allowing some pulmonary venous drainage into the left atrium; an ASD is usually present.

**Partial anomalous pulmonary venous return**

Multiple types of PAPVR exist. The most common is connection of the right pulmonary veins to the right SVC or right atrium, which represents approximately 74% of patients. The next most common type is connection of the right pulmonary veins to the IVC. The least common type is connection of the left pulmonary veins to the left innominate vein or the coronary sinus [144].

**Total anomalous pulmonary venous return**

Four different types of TAPVR exist based on the location of the anomalous connection: supracardiac, cardiac, infracardiac, and mixed (Figure 21.17) [146]. A “stretched PFO” (70–80%) or true ASD (20–30%) is usually present in TAPVR.

**Supracardiac TAPVR**

Supracardiac connection comprises approximately 55% of cases of TAPVR. In this type, pulmonary venous drainage is to the SVC. In the most common form of this lesion, the two pulmonary veins from each lung converge posterior to the left atrium. A vertical vein then arises from the left side of the confluence and usually passes anterior to the left pulmonary artery and the left mainstem bronchus to drain into the left innominate vein, which then drains to the SVC. Pulmonary venous obstruction is unusual, but may occur as a result of either intrinsic narrowing or extrinsic compression of the vertical vein. Although anomalous connection can occur to the SVC via a right-sided vertical vein, this is much less common [144]. A stretched PFO or ASD is present to allow left heart filling; although this constitutes a right-to-left shunt, cyanosis is often mild due to the greater degree of left-to-right shunting.

**Cardiac TAPVR**

The cardiac type of TAPVR accounts for approximately 30% of cases. The pulmonary veins in this type drain into the coronary sinus or right atrium. Obstruction to the pulmonary veins was reported in 22% of patients in a series of TAPVRs to the coronary sinus [147]. The coronary sinus is often “unroofed” prior to its drainage into the right atrium, allowing some pulmonary venous drainage into the left atrium; an ASD is usually present.

**Infracardiac TAPVR**

Infracardiac TAPVR comprises approximately 13% of cases, and is commonly referred to as infradiaphragmatic TAPVR [144]. This type of connection usually involves a confluence of pulmonary veins from both lungs posterior to the left atrium. A descending vein then courses anterior to the esophagus through the diaphragm at the esophageal hiatus [148]. In 70–80% of patients, the descending vein then joins the portal venous system at either the splenic or the confluence of the splenic and superior mesenteric veins [148]. Nearly all patients with infracardiac TAPVR have obstructed pulmonary veins. This obstruction, which may be either intrinsic or extrinsic, can occur at any location along the pulmonary venous pathway. A stretched PFO or ASD is present in essentially all of these patients.

**Mixed TAPVR**

Mixed type TAPVR makes up approximately 2% of cases. This type of TAPVR consists of anomalous connections at two or more levels. The most common connection involves the left pulmonary veins draining into the left innominate vein and the right pulmonary veins draining to the right atrium or the coronary sinus [144]. Pulmonary venous obstruction has also been observed in these types of connections. A stretched PFO or ASD is usually present in this lesion.

**Natural history and pathophysiology**

**Partial anomalous pulmonary venous return**

Partial anomalous pulmonary venous return results in a variable amount of left-to-right shunting that depends on several factors: the number of anomalously draining veins as a percentage of the total pulmonary venous return; the pulmonary lobes or segments from which the anomalous veins originate; the relative resistances of the normally and anomalously drained pulmonary vascular beds; and the compliance of the receiving chambers. The left-to-right
shunt leads to increased pulmonary blood flow and enlargement of the right atrium and ventricle, as well as dilation of the pulmonary artery [144]. Most patients with an isolated single-vein PAPVR and intact atrial septum are asymptomatic and have a normal life expectancy even if left untreated. Those patients with greater than 50% of the pulmonary veins draining anomalously or those with an associated ASD usually remain relatively asymptomatic until the third to fourth decades of life, when progressive symptoms of dyspnea, recurrent bronchitis, hemoptysis, chest pain, and palpitations with supraventricular arrhythmias can occur. These patients may also present with right heart failure or with pulmonary hypertension and cor pulmonale [144].

**Total anomalous pulmonary venous return**

The natural history and pathophysiology of TAPVR depend largely on whether or not pulmonary venous return is obstructed. In the presence of obstructed pulmonary veins, pulmonary venous hypertension exists with associated pulmonary edema. It is commonly confused with intrinsic lung disease when chest radiograph
reveals bilateral infiltrates in the absence of cardiomegaly. Occasionally neonates with hypoxemic respiratory failure placed on extracorporeal membrane oxygenation are subsequently diagnosed with obstructed TAPVR by echocardiography or CT angiography. Pulmonary arteriovenous vasoconstriction occurs as a compensatory mechanism to minimize pulmonary edema. As PVR increases, the right ventricular systolic and end-diastolic pressures increase, resulting in increased right atrial pressure and right-to-left shunting at the atrial level. Progressive systemic hypoxemia ensues, with metabolic acidosis and multisystem organ failure. Left untreated, death occurs in the first few months of life [7,144].

In unobstructed TAPVR, the left-to-right shunt of pulmonary venous blood results in right atrial and ventricular enlargement with pulmonary overcirculation and subsequent right heart failure. The presence or absence of a restrictive interatrial communication is another major determinant in the pathophysiology of TAPVR; 70–80% of infants have only one PFO, which restricts filling of the left atrium and ventricle. This causes tremendous pulmonary overcirculation, right-sided dilation, and minimal left-sided filling, which results in decreased size of the left atrium and ventricle. The abnormal displacement of the interventricular septum along with chronic underfilling of the left ventricle leads to decreased systemic cardiac output. Symptomatic CHF usually develops in the second month of life and may be partially or totally relieved by transvenous balloon atrial septostomy. Patients with a non-restrictive interatrial communication, generally consisting of a secundum type ASD, have a large left-to-right shunt with increased pulmonary blood flow, but if left untreated they may not develop signs of right heart failure or pulmonary hypertension until the third or fourth decade of life [144,149].

**Surgical approaches and outcomes**

Timing of surgical repair of PAPVR is dependent in part on symptomatology. Patients with a single anomalous pulmonary vein with an intact atrial septum may never require surgical treatment. Surgical therapy is generally reserved for those patients with hemodynamically significant left-to-right shunting with Qp:Qs greater than 2:1; patients with recurrent pulmonary infections, especially those associated with Scimitar syndrome; patients having surgical repair of other major cardiac lesions; and patients with anomalous connections that affect surrounding structures by compression or obstruction [144]. Surgical technique for repair of PAPVR varies depending on the specific anatomy present. The repair can consist of a direct anastomosis of the anomalous veins to the left atrium, or more commonly an indirect communication may be developed utilizing a patch to baffie the anomalous veins to the left atrium, while closing the ASD with the same patch. In configurations where the SVC is at risk for obstruction, it may be transected above the anomalous pulmonary veins and translocated to the right atrial appendage (Warden procedure). In cases of PAPVR in which there is a dual connection to the right and left atrium, which often presents as a connection to the right atrium via a vertical vein and to the left atrium as a “dormant” pulmonary vein, the anomalous connection (e.g. vertical vein) can be occluded via transcatheter techniques [150].

Obstructed TAPVR should be corrected emergently at the time of diagnosis [151]. Patients with unobstructed TAPVR with restrictive interatrial communications are urgently palliated with blade and/or balloon atrial septostomies. These patients (and those with unobstructed TAPVR and non-restrictive interatrial communications) can be medically managed for elective surgical repair, usually in the first year of life.

Techniques for surgical repair of TAPVR depend on the specific anatomy involved. In some cases, a period of deep hypothermic circulatory arrest may be necessary. Surgical repair generally includes incision and enlargement of the anomalous pulmonary venous confluence and direct anastomosis with the left atrium [152] (Figure 21.18). Occasionally, a patch is needed to baffle the veins to the left atrium, particularly with cardiac-type defects with drainage to the coronary sinus (Figure 21.19). So-called “sutureless” techniques are intended to reduce the risk of acquired pulmonary vein stenosis by using marsupialization of pericardium or pleura to create the atrial anastomosis [153,154] (Figure 21.20).

Operative mortality for repair of asymptomatic PAPVR approaches zero [155] and in older symptomatic patients has been reported as less than 6% [156]. Operative mortality for patients with TAPVR has historically been significantly higher, but the 30-day mortality over a recent decade at Texas Children’s Hospital was found to be only 7%, and more recently, other institutions have reported similar improvements [157,158]. Risk factors for operative mortality in TAPVR include heterotaxy syndrome and single ventricle [157,159].

**Anesthetic considerations**

The anesthesiologists’ first encounter of the patient with PAPVR may be in the cardiac catheterization laboratory when, during attempted transcatheter closure of an ASD, the presence of an anomalous pulmonary vein is discovered, thereby preventing the utilization of the device. However, the first encounter of the patient with TAPVR may be in radiology, because an increasing number of newborns with suspected TAPVR undergo chest computed tomography or magnetic resonance imaging, which may be superior to echocardiography and angiography in the evaluation of TAPVR [160,161].

Intraoperative considerations for patients with PAPVR are similar to management of ASD. Minimizing pulmonary blood flow by control of ventilation and consideration for early extubation following repair should be the primary goals.

The pre-bypass management of the patient with obstructed TAPVR generally includes maximizing PaO₂.
with ventilatory support, which may include significant levels of positive end-expiratory pressure (PEEP), inspiratory pressures, and FiO2, avoiding metabolic acidosis, and maintaining hemodynamic stability with the use of inotropic medications as necessary. Pre-bypass inhaled nitric oxide is contraindicated because the pulmonary arteriolar dilation and increased pulmonary blood flow in the face of a fixed distal anatomic obstruction will worsen pulmonary mechanics and often paradoxically worsen hypoxemia. TEE is usually contraindicated due to the risk of further compression and obstruction to pulmonary veins even in the presence of non-obstructed TAPVR. Perioperative monitoring of central venous, left atrial, and pulmonary arterial pressures is helpful.

After bypass, nitric oxide should be used empirically in the case of obstructed TAPVR and should be readily

Figure 21.18 Surgical repair of infracardiac total anomalous pulmonary venous return. (A) The vertical vein is ligated near the diaphragm, and pulmonary venous confluence and left atrium are incised. (B) The confluence and the left atrium are anastomosed. IVC, inferior vena cava; VV, vertical vein; LA, left atrium; LLPV, left lower pulmonary vein; LUPV, left upper pulmonary vein (Source: Mavroudis & Backer [167]. Reproduced with permission of Elsevier.)

Figure 21.19 Surgical repair of a cardiac-type total anomalous pulmonary venous connection. (A) Following right atriotomy the coronary sinus, from which pulmonary venous blood anomalously drains, can be seen adjacent to the atrial septal defect (ASD). Incisions are indicated by dashed lines. (B) The coronary sinus is unroofed and brought into continuity with the ASD. (C) The ASD is patched such that the coronary sinus drains to the left atrium. SVC, superior vena cava; Ao, aorta; PA, pulmonary artery; TV, tricuspid valve; RV, right ventricle; CS, coronary sinus; ASD 2°, secundum atrial septal defect; IVC, inferior vena cava; MV, mitral valve; LA, left atrium. (Source: Mavroudis & Backer [167]. Reproduced with permission of Elsevier.)
Sutureless technique for relieving pulmonary venous obstruction in total anomalous pulmonary venous return. (A) The stenotic pulmonary veins are incised. (B) The surrounding pericardium is mobilized. (C) The mobilized pericardium is sutured to the surrounding tissue such that no sutures contact the pulmonary venous incisions. (Source: Mavroudis & Backer [167]. Reproduced with permission of Elsevier.)
distribution may be optimized with the use of pressure control ventilation and by altering PEEP to improve lung compliance.

Following repair, left atrial filling pressures may be elevated due to the small size and low compliance of the left atrium and ventricle. Accepting low blood pressures while weaning from CPB will help to avoid overdistending the “unprepared” left side. Pulmonary artery pressures are frequently equal to, or sometimes greater than, systemic pressures immediately after weaning from bypass. If the right ventricle is functioning adequately, this situation is often well tolerated for short periods as the PVR decreases in the first hour after bypass. Careful fluid management, optimization of heart rate and rhythm, and inotropic support will improve cardiac output. Temporary cardiac pacing may also be helpful. Perioperative dysrhythmias, especially supraventricular tachycardias, occur in as many as 20% of patients. If tolerated, an inovasodilator like milrinone will decrease left ventricular work and improve cardiac output. It is important to recognize that the Frank–Starling curve is very flat in the small, non-compliant left ventricle, and administration of only a few milliliters of fluid may cause the left ventricle to become overdistended and fail.

KEY POINTS: PAPVR AND TAPVR

- PAPVR is often asymptomatic but may be associated with heart failure.
- PAPVR is managed in a similar manner to an ASD.
- TAPVR exists in four subtypes based on the anomalous connection: supracardiac, cardiac, infracardiac, and mixed.
- The pathophysiology of TAPVR is dependent on the presence and degree of pulmonary venous obstruction and the size of the interatrial communication.
- Obstructed TAPVR patients are particularly cyanotic and require 100% oxygen and significant ventilatory support pre-bypass; iNO should be avoided.
- All TAPVR patients are at risk of post-bypass pulmonary hypertension, especially obstructed patients, and iNO should be available.
- TEE may cause or worsen pulmonary venous obstruction.
- The chronically underfilled left ventricle may respond poorly to overloading after repair.

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http://www.wiley.com/go/andropoulos/congenitalheart

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The authors also present evidence that comorbidities persist late after repair. These include truncal valve insufficiency and decreased indices of exercise tolerance (although mean right ventricular ejection fraction and end-diastolic volume were normal in this cohort).

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CHAPTER 22
Anesthesia for Left–sided Obstructive Lesions

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Introduction

Left-sided obstructive lesions of the heart may occur at various anatomic levels and with varying degrees of severity, ranging from a bicuspid aortic valve with minimal hemodynamic compromise to aortic atresia and hypoplastic left heart syndrome (HLHS) with profound hemodynamic derangements. These derangements in systemic blood flow may occur due to obstruction at multiple levels, such as seen in patients with Shone’s complex, or from circumscribed obstruction at a single level, such as in hypertrophic cardiomyopathy, coarctation of the aorta, interrupted aortic arch, subvalvular, valvular, or supravalvular aortic stenosis. Depending on the specific type of left-sided obstruction, the child may be at risk for pulmonary hypertension and/or impaired coronary perfusion during anesthetic care. A clear understanding of the level and degree of the obstruction is therefore important for optimal anesthetic management.

Aortic valve stenosis

Incidence, anatomy, and natural history

The normal aortic valve has three leaflets and an area of 2 cm²/m² body surface area. Although by some estimates, isolated congenital valvular aortic stenosis occurs in only approximately 2 per 10,000 births [1], it is associated with other cardiac lesions in more than 5% of children suffering from congenital heart disease (CHD) and presents with three to four times higher prevalence in males [2]. Valvular aortic stenosis may be associated with aortic coarctation and/or hypoplasia of the ascending and transverse arch due to decreased antegrade blood flow in the fetus, which...
prevent adequate development of these structures. Aortic stenosis (AS) has been described as part of Hunter’s, Hurler’s, and Turner’s syndrome. Structural variations from the customary tricuspid contour of the aortic valve are common and result in a bicuspid or monocuspid appearance of the valvular apparatus, whose formation starts during weeks 5–7 of embryonic development [3,4]. The diseased valve leaflets are gelatinously or myxomatosely malformed and the commissures are often partially fused, leaving a reduced aortic orifice, which can be located eccentrically. Left ventricular myocardial hypertrophy is commonly observed, but non-hypertrophied left ventricular dilation has also been reported [5]. The age of diagnosis, clinical presentation, treatment modality, and timing of intervention depend not only on the degree of valvular obstruction, but also on concomitant cardiac lesions and left ventricular size and function. Only a small minority (approximately 2%) of asymptomatic patients will develop aortic valve dysfunction by adolescence, and progression of the lesion is usually slow [6,7]. Conversely, neonates with ductal-dependent critical AS may present in shock, requiring aggressive resuscitation and emergent intervention.

Pathophysiology
The diagnosis is typically made using transthoracic echocardiography (TTE), which provides comprehensive information regarding valve anatomy, annular size, aortic root diameter, and ventricular function. Continuous-wave mean Doppler gradients adequately predict the peak-to-peak transvalvular gradient as measured during cardiac catheterization, whereas peak instantaneous Doppler gradients slightly overestimate the transvalvular gradient [8,9]. However, depressed left ventricular function can lead to a misleadingly diminished gradient. A Doppler peak systolic instantaneous gradient of less than 50 mmHg is generally considered indicative of mild AS, with peak-to-peak transvalvular gradients of less than 25–30 mmHg. Many of these patients remain asymptomatic throughout childhood and adolescence. Severe AS, on the other hand, signifies by a peak instantaneous Doppler gradient of greater than 65–75 mmHg and peak-to-peak gradients of more than 50–60 mmHg usually presents during the first week of life [10]. In the most severe form of AS, systemic blood flow and coronary perfusion can often be dependent on retrograde blood flow via a patent ductus arteriosus (PDA). After spontaneous ductal closure, affected neonates frequently present with symptoms of significant congestive heart failure, metabolic acidosis, and mitral valve insufficiency, quickly progressing to cardiogenic shock. Aggressive hemodynamic, respiratory, and metabolic resuscitation as well as immediate treatment with prostaglandin E1 are essential to re-establish adequate systemic perfusion. In infants with a less dramatic presentation, left ventricular stroke volume is often maintained for extended periods of time. Normal ventricular wall tension is maintained by concentric ventricular hypertrophy; however, increased left ventricular systolic and end-diastolic pressures can result in impaired subendocardial perfusion and ischemia. In severe cases, this malperfusion leads to the replacement of myocardium by fibrous tissue, termed endocardial fibroelastosis, further impairing ventricular performance and diminishing survival [11–13].

Surgical and transcatheter approaches and outcomes
Treatment options and timing for intervention depend on the acuity of the clinical presentation and the concomitant cardiac abnormalities. Patients with mild AS can be followed conservatively and, if aortic valve repairs or replacements are performed, outcomes are generally excellent [14], especially if achieved without patches [15]. Neonates suffering from critical AS, on the other hand, require immediate intervention. In this population, important consideration is given to the size and adequacy of the left ventricle to tolerate a one- or two-ventricle repair [16]. Anatomic characteristics guiding this decision include patient age, aortic valve size, degree of endocardial fibroelastosis, presence of tricuspid regurgitation, aortic root diameter (ROOT), long-axis dimension of the left ventricle relative to the long axis of the heart (LAR), body surface area (BSA), and mitral valve area (MVA) [12,13]. The Rhodes’ score, which can be used to predict outcome, is calculated according to the formula:

\[ \text{Score} = 14.0(\text{BSA}) + 0.943(\text{ROOT}) + 4.78(\text{LAR}) + 0.157(\text{MVA}) - 12.03 \]

A Rhodes’ score >0.35 predicts with approximately 90% probability that a neonate would survive a two-ventricle repair. The risk for mortality increases when the left ventricular long axis to heart long axis ratio is 0.8 or less, the indexed aortic root diameter is 3.5 cm/m^2 or less, or the indexed mitral valve area is 5.75 cm^2/m^2 or less. If prior to intervention the left ventricular size is considered inadequate to proceed with a biventricular repair, neonates may need to follow a single-ventricle palliation pathway (discussed in Chapter 25).

Given an adequate left ventricular size, the majority of pediatric cardiac centers currently favor percutaneous balloon valvuloplasty as the first treatment option for severe, ductal-dependent congenital AS. Using a retrograde approach, the balloon sheath is most commonly advanced from the femoral, umbilical, or carotid arteries. However, femoral vascular complications are not uncommon using this technique [17]. An alternative, antegrade approach can be used, in which the balloon is usually inserted from the femoral or umbilical veins, via the foramen ovale, into the left atrium and ventricle. If left ventricular function is adequate, administration of a bolus of adenosine (0.3–0.5 mg/kg), rapid right ventricular overdrive pacing (rate of 220–240/min), or an infusion of esmolol (200 μg/kg bolus followed by titrated infusion)
during balloon dilation prevents forceful ventricular contraction against the balloon-occluded left ventricular outflow tract (LVOT) and ejection of the balloon from the aortic position with potential injury to the valve apparatus. In order to avoid post-interventional aortic valve insufficiency, the selected balloon size usually should not exceed the diameter of the aortic root. Using these techniques, severe aortic valve insufficiency is usually avoided in greater than 80% of patients immediately after intervention, and the 5-year mortality typically remains below 20% [17–21]. If the left ventricle is of borderline size, significant aortic insufficiency would disqualify patients from single-ventricle palliation.

Some congenital heart surgeons prefer primary surgical valvotomy of the severely stenotic aortic valve. Advantages of this open approach include direct inspection and commissurotomy of the valve, and the ability to address concomitant cardiac lesions such as PDA, ventricular septal defect (VSD), or aortic coarctation during the same procedure. However, the need for cardiopulmonary bypass (CPB) can increase morbidity for the patient. Historical case series using this approach have demonstrated an operative mortality of 0–18%, 5-year survival of 60–100% and aortic valve competency in greater than 95% of patients, as well as a 10-year freedom from reintervention of greater than 70% following surgical valvuloplasty [18,22–25].

More recently, the Ross procedure, an aortic valve replacement with a pulmonary autograft combined with placement of a homograft in the pulmonary position, has gained popularity (Figure 22.1). It can also be combined with enlargement of the LVOT, which is termed the Ross–Konno procedure. These procedures can be performed in neonates and infants, but have more commonly been carried out in childhood or adolescence. Compared with prosthetic valve replacement, the Ross procedure avoids the need for chronic anticoagulation. Long-term outcomes have been favorable, with greater than 75% freedom from reoperation up to 10 years postoperatively [26–29]. Allograft or prosthetic valve replacement is usually reserved for adolescent patients after completion of the majority of their somatic growth, if they are candidates for chronic anticoagulation.

Emerging experimental treatment options for critical AS or aortic atresia include a fetal transcatheter valvuloplasty [30]. The rationale for intervention, despite the risks for both mother and fetus, is to avoid single-ventricle palliation by preventing the natural progression of severe AS to HLHS. The treatment is based on the assumption that alleviating the restricted blood flow across the aortic valve will lead to improved growth and function of the left ventricle, thereby allowing a postnatal biventricular repair. However, at present, fetal interventions for AS remain highly controversial [31,32]. See Chapter 15 for a further discussion of this emerging treatment option.

Anesthetic considerations

Neonates with critical AS can present with significant metabolic derangement and hemodynamic instability. Anesthetic management is directed toward meeting the increased oxygen requirement of the hypertrophied left ventricular myocardium and optimizing cardiac output. Physiologic goals include maintenance of preload, afterload, and contractility. A normal or, to some extent, decreased heart rate is preferred. Bradycardia, however, is not well tolerated in neonates, whose cardiac output is heart rate-dependent given their fixed stroke volume, even without AS. Anesthetics that decrease systemic vascular resistance and/or increase heart rate must be used with caution given the fact that these hemodynamic alterations may lead to myocardial ischemia and rapid deterioration of the patient’s status. Vasoconstrictors, such as phenylephrine, can be used in this clinical situation. Dysrhythmias are not uncommon during cardiac catheterization and should be treated aggressively.

Inotropic support with a medication such as epinephrine may be required if myocardial function becomes depressed, but must be used with caution given its ability to increase heart rate and myocardial oxygen requirement. In unstable patients, a high-dose opioid
technique will facilitate both balloon valvuloplasty and surgical valvotomy. Occasionally, extracorporeal membrane oxygenation backup is arranged for selected high-risk patients.

**KEY POINTS: VALVULAR AS**

- Neonates may present in shock and require aggressive resuscitation prior to intervention.
- Transcatheter valvuloplasty is usually the treatment of choice in the neonate with severe or critical AS and adequate left ventricular size, with the major technical risk being overaggressive dilatation with resultant aortic valve insufficiency.
- Complications during balloon angiography include profound myocardial depression, bradycardia, asystole, and ventricular fibrillation.
- Anesthetic management with an opioid-based technique often facilitates maintenance of preload, afterload, contractility, and a low-normal heart rate; significant bradycardia should be avoided in the neonate.

### Subvalvular aortic stenosis

**Incidence, anatomy, and natural history**

Subvalvular AS (subAS) is a fixed obstruction occurring within the LVOT and accounts for approximately 1% of patients with CHD. Patients with subAS usually become symptomatic after infancy, with a higher male predilection of 2:1 to 3:1 [33]. Most commonly, the anatomic correlate of the LVOT obstruction is either a thin, discrete membrane of endocardial or fibrous tissue, or a fibromuscular ridge emanating from the crest of the interventricular septum. Less common manifestations include a circumferential, fibromuscular ring that originates from the anterior mitral valve leaflet and a diffuse, tunnel-like fibromuscular obstruction. Other rare causes of subAS include anomalous attachments of mitral valve leaflets or mitral chordae. A variety of congenital heart lesions may exist in association with subAS and include bicuspid valves, AS, VSD, and aortic coarctation (Table 22.1). SubAS can occasionally present in infancy as part of Shone’s complex or following the surgical closure of a VSD, but more commonly, the diagnosis is not made before the end of the first year of life and severity usually increases with age.

**Pathophysiology**

Patients usually present with complaints of orthopnea, dyspnea on exertion, or exertional angina and syncope. A systolic ejection murmur is present, most notable in the left, second, and third parasternal spaces, and a carotid artery thrill can be palpated in a significant number of patients. The diagnosis is confirmed by color Doppler echocardiography, which allows assessment of the degree of stenosis, biventricular enlargement and function, and concomitant mitral and aortic regurgitation. Cardiac catheterization is usually only needed to assess patients with serial obstructions or a tunnel-like stenosis. As the severity of subAS increases with age, progression of the LVOT obstruction may eventually lead to left ventricular diastolic dysfunction and pulmonary venous hypertension. Moreover, abnormal blood flow across the aortic valve can lead to thickening of the valve leaflets, causing valvular AS, left ventricular hypertrophy, damage to the aortic valve, and subsequent aortic insufficiency.

**Surgical and transcatheter approaches and outcomes**

Currently, surgery is favored as an early intervention for LVOT peak pressure gradients exceeding 40mmHg, and consists of fibromuscular resection with or without myectomy through an aortotomy (Figure 22.2). A study comparing early and late surgery in 83 patients with subAS found that the LVOT gradient was successfully reduced in both groups, but that the late surgery group had a much higher recurrence rate at 5 and 10 years (28% and 57%, respectively) compared with the early surgery group (6% and 0%, respectively) [34]. Failure to intervene early also increases the risk of developing aortic regurgitation, which does not necessarily improve following subaortic resection. Transcutaneous balloon dilation is usually ineffective, due to only temporary relief of the stenosis. Surgical complications include newly developed or worsened aortic insufficiency and postoperative atrioventricular heart block. In patients with tunnel-type subAS, an aortoventriculoplasty (Konno procedure) may be required, or, in the presence of aortic insufficiency, an aortic root replacement with a prosthetic valve or a Ross–Konno procedure.

**Anesthetic considerations**

Anesthetic management of subvalvular stenosis aims at maintaining the oxygen requirements of the myocardium and other end organs. Accordingly, the goal is to decrease myocardial oxygen demand and preserve both preload and afterload while maintaining or allowing a slightly

### Table 22.1 Concurrent congenital anomalies in patients with subvalvular aortic stenosis

<table>
<thead>
<tr>
<th>Lesions</th>
<th>Percentage of patients</th>
</tr>
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<tbody>
<tr>
<td>Bicuspid valves</td>
<td>40</td>
</tr>
<tr>
<td>Aortic stenosis</td>
<td>28</td>
</tr>
<tr>
<td>Ventricular septal defect</td>
<td>24</td>
</tr>
<tr>
<td>Coarctation of aorta</td>
<td>12</td>
</tr>
<tr>
<td>Patent ductus arteriosus</td>
<td>12</td>
</tr>
<tr>
<td>Atrial septal defect</td>
<td>4</td>
</tr>
</tbody>
</table>
decreased heart rate. In this regard, the anesthetic management of the patient with subAS is very similar to that for valvular AS.

**KEY POINTS: SUBVALVULAR AS**

- Subvalvular AS usually consists of a discrete membrane in the LVOT presenting after infancy, but can also be seen as part of multi-level left-sided obstruction in patients with Shone’s complex.
- Early surgical membrane resection with or without myectomy is favored over transcatheter approaches for an LVOT pressure gradient >40 mmHg.
- Hemodynamic goals during anesthetic management are similar to AS; maintaining preload and afterload, and allowing a slightly decreased heart rate.

**Supravalvular aortic stenosis**

**Incidence, anatomy, and natural history**

Congenital supravalvular AS is the least common fixed obstruction of the LVOT, accounting for less than 0.05% of CHD. However, caused by abnormalities in the elastin gene (ELN), supravalvular AS occurs in up to two-thirds of patients with Williams–Beuren syndrome, also known as Williams syndrome, and as part of familial supravalvular AS [35–38]. The outflow tract obstruction frequently arises as a concentric narrowing of the ascending aorta at the superior margin of the sinuses of Valsalva, creating a typical hourglass deformity of the aorta [39]. Other manifestations include a diffuse narrowing along the entire ascending aorta or a fibrous semicircular membrane at the sinotubular junction. Supravalvular AS is a progressive disease, usually diagnosed after infancy, but may present earlier in life in patients with Williams syndrome. Coronary artery involvement, which is common in children with Williams syndrome, may include a reduction of the left coronary artery ostial size, ostial obstruction by fusion of the aortic cusp to the supravalvular ridge, or diffuse narrowing of the left coronary artery (Figure 22.3). In cases of mild supravalvular AS, one case series found spontaneous improvement in the obstruction with time in 16% of patients and complete resolution in another 12% [40].

**Pathophysiology**

Supravalvular AS’s underlying mechanism in Williams syndrome is an elastin arteriopathy, leading to a lack of elastic tissue in the walls of large arteries, increased amounts of collagen, and hypertrophy of smooth muscle cells [41]. Accordingly, pulmonary artery stenosis is also observed in over 30% of these patients, which can lead to biventricular hypertrophy [38]. Supravalvular AS may also be associated with a bicuspid aortic valve and aortic valvular stenosis in up to 50% of patients [42]. Concentric left ventricular hypertrophy can lead to myocardial ischemia, which is exacerbated by concomitant coronary artery stenosis. The risk of sudden death may only be slightly increased in patients with sporadic supravalvular AS, but is significantly higher in patients suffering from Williams syndrome than in the general population [43,44]. A low-pitched, crescendo–decrescendo, systolic murmur is commonly heard at the base of the heart, radiating to the
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Figure 22.3 Representative angiogram of a patient with Williams syndrome, demonstrating supravalvular aortic stenosis (black arrow) and left coronary artery ostial stenosis (white arrow). (A) Anteroposterior view. (B) Lateral view. Peak systolic gradient during catheterization was 70 mmHg. (Source: Robert Beekman, MD. Reproduced with permission.)

right carotid artery. The diagnosis of supravalvular AS is routinely made using two-dimensional echocardiography, and Doppler echocardiography can be used to determine the pressure gradient across the ascending aorta. Electrocardiograms usually show left ventricular hypertrophy with special attention given to potential ischemic ECG changes. Patients with Williams syndrome, occurring in approximately 1 in 20,000 live births, are easily recognized due to their characteristic facial dysmorphisms; common features include a wide mouth with full lips, micrognathia, dental malocclusion, widely spaced teeth, a short nose with a flat nasal bridge, and a long philtrum. They may also suffer from arterial hypertension, hypercalcemia with nephrolithiasis, esotropia, a hoarse voice, joint hyperelasticity, and sensorineural hearing loss. Although patients often exhibit cognitive impairment, they commonly have a characteristic desire for conversation and company with a lack of social inhibition [38,45]. The suspected diagnosis of Williams syndrome can be verified even in neonates who do not yet exhibit the characteristic features, using genetic testing for karyotype and the fluorescent in situ hybridization (FISH) test for the 7q11.23 elastin gene deletion [46].

Surgical and transcatheter approaches and outcomes

Infants with a peak pressure gradient of less than 20 mmHg across the supravalvular stenosis often remain stable and do not require intervention; however, a peak instantaneous pressure gradient of greater than 75 mmHg is usually an indication for surgical intervention [40]. Surgical techniques for repair of supravalvular stenosis include patch aortoplasty with one (Figure 22.4) or multiple patches [47], complete excision of the stenotic ring with end-to-end anastomosis, or the Ross or Ross–Konno procedures [42,48]. Significant coronary ostial obstruction may be relieved by a patch enlargement of the coronary os, excision of the obstructing aortic leaflet, or coronary artery bypass grafting [49]. Concomitant pulmonary artery stenosis in many patients with Williams syndrome is frequently addressed by balloon dilation of the right ventricular outflow tract stenosis prior to surgical repair of the LVOT obstruction.

Anesthetic considerations

Supravalvular AS shares many of the pathophysiological characteristics and anesthetic management requirements of valvular and subvalvular stenosis. However, due to the potential combination of supravalvular AS, left ventricular hypertrophy, right ventricular outflow tract obstruction, and coronary artery disease, patients with Williams syndrome can be at significantly increased risk for anesthesia-related complications. Accordingly, several reports have described perioperative fatalities in these patients, ranging from events during anesthesia induction or intubation to postoperative complications [43,50–54]. The majority of these reported events seemed to be caused by myocardial ischemia. Maintaining afterload at slightly elevated levels is therefore paramount to preserve coronary perfusion pressure. Volatile anesthetics must be used with caution due to their myocardial depressive and
vasodilatory effects. Intramuscular premedication with ketamine may facilitate the establishment of intravenous access, and high-dose opioid techniques may accomplish the anesthetic goals. However, significant increases in heart rate, which can occur following administration of ketamine or vagolytic agents, are not well tolerated and need to be treated aggressively. It must be emphasized that the coronary arteries are frequently significantly involved, being partially obstructed or “hooded” from the abnormal surrounding connective tissue in the aorta, and that the degree of coronary obstruction often does not correlate with the severity of the supravalvular AS. Other anesthetic complications, such as difficult mask ventilation or difficult tracheal intubation, may arise due to the concomitant facial deformities in this syndrome. Moreover, the potential development of abnormal skeletal muscle tissue with lipid deposits may lead to an increased sensitivity to muscle relaxants, thus warranting close monitoring of neuromuscular blockade [55]. Additional sources of perioperative morbidity include their predisposition to renal insufficiency and arterial hypertension, which need to be appropriately addressed in the anesthetic plan.

**KEY POINTS: SUPRAVALVULAR AS**

- Supravalvular AS occurs in two-thirds of patients with Williams syndrome and can be accompanied by coronary and ostial stenoses, substantially increasing the risk of coronary events and sudden death.
- Maintain preload and afterload at high-normal levels to preserve coronary perfusion pressure, and maintain heart rate and contractility at low-normal levels.
- Avoid anesthetic techniques that produce significant decreases in preload and afterload, e.g., high doses of volatile anesthetics and/or propofol.
- Tachycardia is not well tolerated in patients with significant coronary stenosis and must be treated aggressively.

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**Figure 22.4** Repair of supravalvular aortic stenosis. (A) External appearance. (B) Coronal plane view of the defect. (C) Inverted Y incision in the ascending aorta. (D) Placement of an autologous pericardial patch. (Source: Chang et al. [21]. Reproduced with permission of Lippincott, Williams & Wilkins.)
Hypertrophic cardiomyopathy

Incidence, anatomy, and natural history

Hypertrophic cardiomyopathy (HCM) is a cardiac disorder with significant heterogeneity of etiology, anatomic findings, and clinical presentation; it occurs in about 0.2% of the population [56,57]. The annual mortality in tertiary care centers is 3–4% overall and up to 6% in children, while in the unselected population, the mortality rate may be less than 1% [57]. Over the past decade the increased availability of genetic and metabolic testing has improved the ability to identify the underlying etiology of HCM. The cause of HCM can be divided into four diagnostic categories: familial, metabolic, syndromic, and idiopathic [58]. In one single-center pediatric study, an affected family member, positive HCM gene panel mutation, metabolic disease, or genetic syndrome were identified in over 80% of patients with HCM. In children presenting at less than 1 year of age, a metabolic cause such as mitochondrial disease or Pompe disease was present in almost 50% of patients [58]. In Noonan syndrome, a genetic disorder commonly associated with cardiac disease, approximately 15–20% of children have HCM, with less favorable outcomes than children with non-syndromic HCM [59,60].

The characteristic gross morphologic feature in HCM is a hypertrophied and non-dilated left ventricle, and the absence of other disease processes capable of causing this degree of hypertrophy (e.g., AS). There is significant heterogeneity with regard to the location and degree of cardiac hypertrophy, and in fact, even first-degree relatives with familial HCM often exhibit different patterns of hypertrophy [61,62]. Myocardial hypertrophy may occur in the anterior, posterior, and/or basal regions of the ventricular septum, and in the ventricular free wall. The hemodynamic severity is dependent on the particular region where hypertrophy is most prominent: significant hypertrophy of the anterior region of the ventricular septum compared with the posterior septum more commonly causes subaortic outflow obstruction [63]. Echocardiography is extremely helpful in determining the extent, location, and severity of the disease. Quantitative echocardiographic findings in patients with HCM include increased left ventricular wall thickness, decreased left ventricular end-diastolic cavity size, and increased left ventricular fractional shortening [64]. Other important findings include the presence and severity of LVOT obstruction, systolic anterior motion of the mitral valve, and mitral regurgitation [65].

The natural history of this disease is dependent on multiple factors, including the underlying etiology, age at presentation, clinical signs and symptoms, and the presence of other co-morbidities. Most patients with HCM, and neonates in particular, often remain asymptomatic for a long period of time. Many patients are not diagnosed until they present with symptoms of congestive heart failure, cardiac rhythm disturbances, or syncope, or following a near-death cardiac event [57]. HCM has become the leading cause of sudden cardiac death in young athletes usually occurring in individuals older than 35 years [61,66]. Even when the diagnosis is made prior to a catastrophic event, the clinical course of the disease is inconsistent and dependent on whether the HCM is obstructive or non-obstructive. If obstructive, more than 25% of infants will develop symptoms of congestive heart failure manifested by feeding intolerance or failure to thrive [60]. Adult patients with HCM are at substantial risk for the development of atrial fibrillation, which can cause significant hemodynamic impairment due to its negative effects on ventricular preload [67].

Pathophysiology

Hypertrophic cardiomyopathy is most commonly caused by mutations in genes encoding proteins of the myocardial sarcomere, and in fact over 50 mutations causing the disease have been identified, making it one of the most widespread genetic diseases of the myocardium. Depending on the specific mutation, abnormalities in the protein may lead to ineffective contraction of the sarcomere and the development of myocyte hypertrophy [57]. The histology of the left ventricle is remarkable for disarray of the hypertrophied cardiac muscle cells, myoccardial scarring, and thickened walls in small intramural coronary arteries causing luminal narrowing [63,68]. Although fiber disarray is present even in normal hearts, the extent to which this happens in the heart with HCM is significantly increased [69]. A minority of patients may progress to a secondary phase characterized by wall thinning in areas of previous hypertrophy, enlargement of cavity size, and impairment of ventricular function, a phenomenon likely related to myocardial ischemia and necrosis [63].

Hypertrophic cardiomyopathy also presents in infancy without sarcomeric protein gene mutations, such as in infants of insulin-dependent diabetic mothers or in patients with Pompe disease. Pompe disease represents a glycogen storage disease type II (GSD-II) which is a rare autosomal recessive disorder occurring in 1 out of 40,000 live births, in which lysosomal glycogen accumulates in both cardiac and skeletal muscle due to a deficiency of acid α-glucosidase [70,71]. Children presenting with the infantile form of this disease exhibit severe HCM, and, untreated, often die in the first year of life from respiratory or cardiac complications. Therapy with long-term intravenous recombinant α-glucosidase often leads to significant resolution of the cardiac hypertrophy and skeletal muscle weakness [72] Infants presenting for surgery prior to therapy with recombinant human α-glucosidase are at high risk for anesthetic complications [73]. In a retrospective review, 6% of patients with infantile-onset Pompe disease receiving anesthetics developed an arrhythmia or cardiac arrest soon after induction of anesthesia [74]. Two-thirds of these events were attributed to the use of sevoflurane or propofol.
The most common finding in the patient with HCM is a hyperdynamic left ventricle with abnormal diastolic relaxation and compliance; LVOT obstruction is present in no more than 25% of patients [75]. The degree of outflow tract obstruction is a dynamic process and may be reduced or abolished by decreasing myocardial contractility, increasing preload, or increasing afterload. Conversely, the dynamic obstruction is increased during periods of increased ventricular contractility or sympathetic stimulation, as for instance, with exercise. The outflow tract gradient is felt to be caused in part by anterior movement of the mitral valve toward the ventricular septum during early systole, and more likely to occur in the setting of a hypertrophied anterior septum [75]. Anterior movement of the mitral valve may interfere with optimal valve closure, causing mitral regurgitation, occurring more commonly in the setting of LVOT obstruction. The combination of severe left ventricular hypertrophy, LVOT obstruction, and abnormalities of the intramural coronary arteries all place these patients at increased risk of myocardial ischemia and ventricular arrhythmias.

**Surgical and transcatheter approaches and outcomes**

Treatment modalities for HCM include medical therapy, surgical therapy, the use of pacing and/or implantable cardioverter-defibrillators, and cardiac transplantation. Aggressiveness of therapy in any given patient depends on the risk factors for morbidity and mortality. Identified risk factors for patients with HCM include family history of sudden death or syncope, extreme septal hypertrophy, and LVOT obstruction [76,77]. Asymptomatic patients with HCM may not require any therapy. When medical therapy is initiated, it usually consists of either a β-blocker or calcium-channel blocker, and can be guided by treadmill exercise testing or patient symptoms [57]. Another treatment option is dual-chamber pacing, which has been used as an alternative to surgery with mixed results. Although pacing has been shown to be of benefit in some patients, randomized controlled trials showing long-term improvement in outcomes are lacking. For patients at high risk for sudden death, such as those with documented sustained ventricular tachycardia/ventricular fibrillation, significant family history of sudden death, or a high-risk mutation, most centers will now place an implantable cardioverter-defibrillator [57].

Indications for surgical intervention include a left ventricular outflow gradient >50 mmHg and significant symptoms such as dyspnea, angina, or syncope unresponsive to medical therapy. Septal myectomy is an effective treatment in both pediatric and adult patients [63,65]. In pediatric patients with HCM undergoing septal myectomy at the Mayo Clinic over a 28-year period, there were no early deaths and survival rates at 5 and 10 years were 97% and 95%, respectively. Late follow-up was remarkable for 96% of patients remaining in New York Heart Association (NYHA) functional class I or II [76]. The surgical approach is commonly transaortic, and often technically challenging in the smaller child. Transesophageal echocardiography (TEE) can be used to aid in the assessment of intracardiac anatomy before resection and of the adequacy of resection following myectomy. Despite an excellent surgical result with minimal residual left ventricular outflow gradient, these children remain at risk for cardiac arrhythmias and sudden death [76]. Patients with congestive heart failure, myocardial ischemia, and/or life-threatening arrhythmias, despite optimal medical and surgical therapies, may be considered for cardiac transplantation.

**Anesthetic considerations**

Patients with HCM are at significant risk for cardiac complications during anesthesia and surgery. Although there are few studies looking at the pediatric population with HCM, one adult study was remarkable for 40% of patients experiencing at least one perioperative adverse cardiac event [78]. Predictors of adverse outcome included major surgery and duration of surgery. To avoid hemodynamic instability, anesthetic management should be tailored toward maintaining preload and afterload, decreasing myocardial contractility, and avoiding tachycardia. Maintenance of normovolemia prior to induction is vital, and, if necessary, an intravenous catheter should be inserted prior to surgery. While halothane meets many of the hemodynamic goals and has been well tolerated in such cases, it is no longer available [79]. Sevoflurane and desflurane, on the other hand, may cause significant increases in heart rate and reductions in systemic vascular resistance, and should be used with caution. High-dose opioid anesthesia provides stable hemodynamics and maintenance of a normal to low heart rate. Remifentanil, a short-acting potent opioid administered by continuous infusion, may be an excellent choice when extubation of the trachea following surgery is planned. For patients not already on β-blocker therapy, esmolol can be used in the perioperative period to control heart rate and reduce cardiac contractility.

Depending on the procedure and severity of HCM, arterial vascular access and central venous access may be indicated. Patients with a critical LVOT gradient may benefit from pre-induction placement of an arterial line for close monitoring of systemic blood pressure during anesthetic induction. However, one must carefully judge whether the increased anxiety and pain caused by the procedure might precipitate an adverse event. The placement of a central venous line for this disease state is not a trivial task, and the patient must be closely monitored for the occurrence of an atrial dysrhythmia. Rapid treatment of dysrhythmias is important, as hemodynamics may deteriorate swiftly. Central venous pressure may be significantly elevated in the patient with HCM due to the hypertrophied non-compliant ventricle.
Coarctation of the aorta

Incidence, anatomy, and natural history
Coarctation of the aorta denotes a narrowing of the aortic lumen and is most often located just distal to the opening of the left subclavian artery at the point of insertion of the ductus arteriosus. Although usually presenting as a discrete narrowing, the coarctation can also be a long-segment stenosis or be associated with hypoplasia of the transverse aortic arch. Up to 8% of patients with CHD have an aortic coarctation, which is more prevalent in males than females by a 1.5:1 ratio [2,80]. The etiology of the coarctation is a folding of the medial tissue of the aortic wall such that it encroaches upon the aortic lumen. When the coarctation is severe with limited anterograde flow from the transverse arch, blood flow to the distal aorta may be entirely dependent on a PDA. If the coarctation segment remains uncorrected for a prolonged period of time, collateral blood flow will develop, thus allowing for adequate perfusion distal to the aortic obstruction. Other congenital cardiac anomalies are present in about one-half of patients with aortic coarctation and include ventricular septal and atrioventricular canal defects, valvular AS, and subvalvular AS.

If untreated, the natural history of aortic coarctation is primarily related to the severity of the obstruction. Over 90% of untreated patients with coarctation of the aorta die by the age of 50 [81]. Even with surgical repair, patients with aortic coarctation demonstrate an increased predilection for hypertension, coronary artery disease, stroke, heart failure, and ruptured aortic and cerebral aneurysms. Over 50% of patients have arterial hypertension at long-term follow-up, which is not necessarily related to the presence of a recurrent stenosis [82]. Patients who have undergone aortic coarctation repair during infancy without residual stenosis also exhibit abnormal left ventricular diastolic function and aortic elasticity as adults [83].

Pathophysiology
The neonate with a severe coarctation generally presents during the first few weeks of life with congestive heart failure, left ventricular systolic dysfunction, and, in some cases, cardiogenic shock. The closure of the ductus arteriosus causes an acute increase in left ventricular afterload, elevation of left ventricular end-diastolic pressure, reduction in stroke volume, pulmonary venous congestion, and pulmonary artery hypertension [2]. The infant with a less severe coarctation may exhibit tachypnea and failure to thrive. Still, the asymptomatic child with an unrecognized coarctation is at increased risk for developing systemic hypertension proximal to the coarctation and subsequent left ventricular failure.

The diagnostic feature of aortic coarctation is a systolic blood pressure difference between the upper and lower extremities. TTE [84] using a suprasternal long-axis view typically shows a localized narrowing (“posterior shelf”) just distal to the left subclavian artery, and Doppler analysis aids in assessing the severity of the coarctation. Evaluating the heart for other associated lesions is important. Magnetic resonance imaging (MRI) and computed tomography (CT) angiography with three-dimensional reconstruction are other modalities used to image the aortic arch, and are more commonly utilized in older children and adults where imaging by TTE is often suboptimal. A study comparing CT angiography with TTE for diagnosis of coarctation demonstrated that CT angiography was the more sensitive test (100% vs. 87.5%) [85]. Drawbacks to these modalities include the use of ionizing radiation with CT angiography, and the necessity for anesthesia or sedation for MRI in younger children.

Surgical and transcatheter approaches and outcomes
Therapeutic options for aortic coarctation include surgery, balloon dilatation, and placement of endovascular stents. However, there is currently considerable uncertainty regarding the optimal long-term treatment strategy. At the present time, neonates and infants are thought to have a superior outcome with surgical repair, while older patients may benefit from balloon dilatation with or without stenting as the initial therapy [86]. A retrospective study comparing balloon angioplasty and surgery as the initial therapy for neonatal coarctation showed that over 80% of patients undergoing balloon angioplasty subsequently required surgery or repeat balloon dilatation, while less than 20% of patients undergoing surgery required reintervention [87]. Another study comparing outcomes in children undergoing balloon angioplasty for native coarctation found that the incidence of restenosis and aneurysm formation was significantly increased in children <1 year of age [88]. The options for surgical repair include a subclavian flap aortoplasty, a resection of the narrowed portion of the aorta with a traditional end-to-end anastomosis, an

KEY POINTS: HYPERTROPHIC CARDIOMYOPATHY

- Hypertrophic cardiomyopathy is a heterogeneous condition caused by multiple factors including mutations in genes encoding sarcomeric proteins, metabolic disorders, and genetic syndromes such as Noonan syndrome.
- Characteristic anatomic features include a hypertrophied left ventricle with hyperdynamic systolic function and abnormal diastolic relaxation.
- Hypertrophic cardiomyopathy currently is the leading cause of sudden death in young athletes.
- Anesthetic considerations include maintaining preload at high-normal levels, decreasing myocardial contractility, and avoiding tachycardia.
aortic arch advancement technique (extended end-to-end or end-to-side reconstruction), or an interposition tube graft. The aortic arch advancement technique is used when transverse arch hypoplasia is present, and requires proximal extension of the anastomosis onto the underside of the transverse arch up to the level of the innominate artery [89] (Figure 22.5). This approach requires placement of a cross-clamp just distal to the innominate artery, placing the patient at risk for cerebral hypoperfusion. Other perioperative complications from surgical repair of coarctation include recurrent laryngeal nerve or phrenic nerve injury, chylothorax, bleeding, and rarely paraplegia (0.4%) [90].

Restenosis after surgical repair of aortic coarctation is not uncommon, with an incidence that varies widely depending on the surgical technique, age of patient at time of repair, definition of recurrence, and length of follow-up [91]. A study examining long-term complications in a cohort of patients up to 27 years after repair found a restenosis rate of 11%, with restenosis defined as a systolic brachial–ankle blood pressure difference of greater than 20 mmHg [82]. Earlier studies showed a higher incidence of recoarctation if the operation was performed in the first 3 years of life; the recurrence rate was <3% if performed afterward [92]. A more recent study utilizing MRI in adults that had undergone aortic coarctation repair during childhood found recoarctation and local aneurysm formation in 48% and 21% of patients, respectively [93]. Current surgical techniques emphasizing aggressive excision of ductal tissue and the use of an extended end-to-end anastomosis in the setting of arch hypoplasia may lead to a lower incidence of restenosis. Because of the significant prevalence of hypertension and other long-term sequelae following coarctation repair, many centers aggressively treat even mild recurrent stenosis in the interventional catheterization suite.

Figure 22.5 Two surgical approaches for repair of coarctation of the aorta. (A) Resection of coarctation with end-to-end anastomosis. (B) End-to-side, or aortic arch advancement technique. (Source: Chang et al. [21]. Reproduced with permission of Lippincott, Williams & Wilkins.)
The use of balloon angioplasty for initial treatment of discrete aortic coarctation in children frequently provides excellent immediate hemodynamic results [84,86,94]. Reluctance to use this approach in some centers is related to concerns about restenosis and aneurysm formation, which occur in 10–20% and 5–10% of patients, respectively [85]. Approximately 25% of children undergoing an initial balloon angioplasty will require a reintervention within 2 years [84,86]. Balloon angioplasty is generally accepted as the first-line therapy for restenosis following surgical repair of aortic coarctation, providing excellent immediate and long-term results [91,95,96]. In approximately 80% of cases, the residual systolic pressure gradient can be reduced to less than 20 mmHg. Repeat balloon angioplasty or surgery is required in about 25% of these patients due to restenosis [91]. Complications related to balloon angioplasty include femoral artery thrombosis, aortic rupture, and stroke. The risk of femoral artery injury is greater in the smaller child. An increased mortality risk has been reported for patients undergoing angioplasty for recurrent coarctation versus native coarctation [95].

Balloon-expandable endovascular stents provide an effective therapy for treatment of native or recurrent coarctations occurring after surgery or balloon angioplasty [97–100] (Figure 22.6). In a study including 565 procedures from multiple institutions, 97.9% of patients had a successful reduction in the coarctation gradient at the time of the procedure [97]. Stents have been successfully used to treat patients with both discrete coarctation and transverse arch hypoplasia. Intermediate follow-up in patients receiving stents shows that the incidence of restenosis is reduced compared with balloon angioplasty [98–100]. Stents allow for future redilation to a larger size to accommodate the growth of the child. This therapy is limited by the need for a large sheath (8–9 Fr) in the femoral artery, and is thus not utilized in some centers until a child reaches a certain size. Endovascular stents have been placed in smaller children using the carotid artery, thus requiring a surgical procedure to place a sheath in this vessel. Complications related to stent placement include aneurysm formation, aortic dissection, stent migration, balloon rupture, femoral artery injury, and stroke, and may occur in as many as 15% of patients [88]. The use of covered stents, currently investigational in the United States, may decrease the risk of arterial wall injury, particularly in older patients with increased aortic fragility. In a recent single-center study, 56 patients (11–56 years of age) were treated with covered stents for complex coarctation of the aorta with a decrease in the systolic gradient from a mean of approximately 50 to around 5 mmHg [101]. Complications included one patient who was found to have an aortic dissection, which was treated conservatively, and one death during the postoperative period felt to be related to pre-existing left ventricular dysfunction. Redilation of the stent due to a subsequent increase in the gradient was required in four patients.

**Anesthetic considerations**

The medical management of infants with severe coarctation consists of inotropic support and diuretics. In infants younger than 1 month, intravenous prostaglandin is utilized to reopen the ductus arteriosus. Intubation may be necessary to decrease the work of breathing and reduce

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**Figure 22.6** (A) Angiograms of a 12-year-old patient with a native aortic coarctation (black arrow) and a long, moderately hypoplastic isthmus before placement of a stent. Note the multiple arterial collaterals (white arrows). (B) Angiogram after stent placement. The systolic gradient was reduced from 30 to 3 mmHg following stent placement. (Source: Robert Beekman, MD. Reproduced with permission.)
left ventricular demand. Metabolic acidosis should be corrected to improve left ventricular function.

The anesthetic management of the patient presenting for surgical repair of coarctation of the aorta should include a right-sided upper extremity arterial catheter in addition to the usual anesthetic monitors. The placement of the right intra-arterial catheter ensures that blood pressure will be monitored during the phase of the operation when the aorta, left carotid artery, and left subclavian artery may be clamped or compressed. The use of cerebral near-infrared spectroscopy (NIRS) for continuous monitoring of bi-hemispheric cerebral oxygenation allows the anesthesiologist to identify cerebral hypoperfusion related to aortic cross-clamp position or inadequate cardiac output [102]. Central venous access may be indicated for initiation of inotropic support.

Induction of anesthesia can be accomplished by either intravenous or inhalational anesthesia; however, in the child with significant ventricular dysfunction, an opioid-based induction may be preferable. The surgical repair is usually performed through a left thoracotomy, and lung retraction can impact ventilation. Close monitoring of arterial blood gases for adequacy of ventilation is vital. Inadequate ventilation causing severe acidosis in a critically ill neonate can worsen cardiac function and lead to cardiac arrest. There have been reports that infants with a core temperature greater than 38°C are at increased risk for spinal cord ischemia. Many centers choose to allow the child to cool to about 35°C in order to protect against this complication [103]. The application of the aortic cross-clamp usually causes upper body hypertension, while blood flow to the lower body and spinal cord becomes reliant on collateral flow that can vary depending on the anatomy of collateral blood vessels and on arterial pressure. It is possible that the failing ventricle may be unable to maintain an appropriate cardiac output after cross-clamp placement due to the sudden increase in afterload, in which case an inotropic agent may need to be administered [104]. If myocardial function is adequate, volatile anesthetics can be used to limit arterial hypertension during aortic cross-clamp. However, during completion of the vascular anastomosis, the dose of volatile anesthetic is usually reduced and fluid boluses may be administered in anticipation of systemic hypotension following release of the aortic cross-clamp.

The early postoperative period is often complicated by the onset of hypertension, which may be exacerbated in the setting of poor pain control. Greater than one-half of patients who undergo repair of a coarctation experience significant increases in blood pressure for up to 2 weeks [105]. It has been postulated that the increase in blood pressure may be secondary to stimulation of the sympathetic system distal to the anastomotic site, with subsequent increases in plasma renin activity. Untreated hypertension can result in mesenteric arteritis [106]. Hypertension in the acute perioperative period is usually treated with infusions of sodium nitroprusside or esmolol. Some centers utilize continuous epidural analgesia for control of pain following coarctation repair. Purported benefits of this technique compared with intravenous opioid therapy include better pain and blood pressure control and improved respiratory mechanics. Others avoid epidural analgesia because of the potential for confusion as to etiology in the rare instance of paraplegia after coarctation repair.

### Key Points: Coarctation of the Aorta

- Coarctation of the aorta is commonly located immediately distal to the takeoff of the left subclavian artery and may be accompanied by hypoplasia of the transverse aortic arch.
- The neonate with aortic coarctation may present with congestive heart failure due to left ventricular dysfunction and may require inotropic support and mechanical ventilation prior to surgical repair.
- Maintaining myocardial contractility and normal blood pressure during the aortic repair is important to provide perfusion to the spinal cord and subdiaphragmatic viscera.
- Patients with a history of repaired aortic coarctation are at increased risk for systemic hypertension, left ventricular systolic and/or diastolic dysfunction, and coronary artery disease.

### Interrupted or Hypoplastic Aortic Arch

**Incidence, anatomy, and natural history**

An interrupted aortic arch (IAA) exists in about 1% of patients with congenital malformations of the heart. The interruption may be divided into three anatomical variants: type A, which is characterized by a location just distal to the left subclavian artery (25% of IAA); type B, located in the space between the left subclavian artery and the left common carotid artery (70% of IAA); and type C, between the innominate and left common carotid arteries (5% of IAA) [106,107] (Figure 22.7). The majority of patients with a type B IAA have DiGeorge syndrome (chromosome 22q11.2 deletion) [108]. Common features in the infant with DiGeorge syndrome include hypocalcemia, an absent thymus, and anomalies of the ears, face, and palate.

All types of IAA have a high incidence of associated congenital cardiac anomalies. A VSD is most prevalent and present in greater than 90% of type B interruptions and more than 50% of type A interruptions [109]. The VSD is usually posteriorly malaligned, leading to posterior deviation of the conal septum into the LVOT. Other concomitant cardiac defects include bicuspid aortic valve, truncus arteriosus, transposition of the great arteries, and double outlet right ventricle [110]. LVOT obstruction occurs in as many as 57% of patients with IAA, and is more commonly associated with type B interruption and anomalous right subclavian artery [111,112].
In children born with IAA, the prognosis for survival without surgical intervention is poor, with as many as 90% of patients dying within the first year of life [113]. Those who survive past the first year develop a collateral circulation that allows for adequate lower-body perfusion despite the aortic interruption [114]. Even with surgical intervention during infancy, many children require subsequent procedures later in life, the most common indications being aortic arch obstruction and LVOT obstruction [115]. Accordingly, IAA is now considered a chronic disease and close follow-up by a congenital cardiologist is indicated throughout the patient’s life [116].

Pathophysiology
Neonates suffering from IAA often remain asymptomatic initially after birth, but over the course of a few days or weeks they can become precipitously ill following closure of the ductus arteriosus. As the duct constricts, blood flow to the lower body becomes compromised, drastically increasing the risk of shock. Congestive heart failure may develop as a greater proportion of blood flow is directed to the pulmonary circulation. Rapid diagnosis accompanied by initiation of prostaglandin therapy, treatment of metabolic acidosis, and respiratory and/or myocardial support may be life-saving. Fetal echocardiography has led to improvements in early diagnosis and a reduction in the number of neonates presenting with circulatory collapse. Unlike the neonate with severe coarctation of the aorta, differential oxygen saturations between the right upper and lower extremities may not be present due to mixing of blood through a VSD.

The diagnosis of IAA can usually be established with TTE, and cardiac catheterization is usually not indicated. MRI and CT angiography have also been used to delineate complex arch anatomy. Careful evaluation for additional cardiac anomalies, including the presence of LVOT obstruction, is important.

Surgical and transcatheter approaches and outcomes
Surgical strategies for treatment have varied. A two-stage approach involving initial repair of the aortic arch through a left thoracotomy accompanied by pulmonary artery banding allows for palliation without the use of CPB. This approach provides only limited exposure of the proximal aorta and does not allow the surgeon to address other coexisting lesions, such as LVOT obstruction. A primary one-stage repair using a midline sternotomy and CPB is now favored. This approach provides optimal exposure for aortic arch repair, and the ability to close the VSD and address other associated lesions. A recent multicenter study suggested that surgical approaches other than direct anastomosis with patch augmentation of the IAA may increase the risk for future aortic arch reintervention [117]. However, one center recently reported that 100% of patients required no arch reintervention at 5 years after direct anastomosis without patch augmentation when the descending thoracic aorta was circumferentially mobilized, ductal tissue aggressively excised, and a wide anastomosis made between the descending aorta and the posterior aspect of the distal ascending aorta [118] (Figure 22.8).

Until the last decade, major aortic arch surgery required the use of deep hypothermia with circulatory arrest, which
may adversely impact long-term neurodevelopmental outcomes [119]. Many centers now use antegrade cerebral and myocardial perfusion during arch repair providing continuous delivery of oxygen to the brain and minimizing myocardial ischemic time (see Chapter 7). Over the next decade, studies should elucidate whether these techniques improve survival and reduce long-term morbidities.

Interrupted aortic arch continues to be associated with significant mortality during the perioperative period and subsequent long-term follow-up. A study reporting outcomes from 33 institutions between 1987 and 1997 found an overall survival of 60% at 21 years after initiation of study [116]. One-third of patients in this study required one or more subsequent arch and/or LVOT procedures. Other studies found an overall perioperative mortality rate for procedures done since 1990 of 12%, compared with an overall mortality rate of 42% prior to 1985 [120,121]. One-month survival of >92% following IAA repair has been reported at a number of centers [112,118]. Risk factors reported to be associated with increased mortality include low birth weight, type B IAA, other major associated cardiac anomalies, DiGeorge syndrome, LVOT obstruction, and an episode of circulatory collapse prior to repair [110,117,118]. Several studies have questioned whether LVOT obstruction is a risk factor for increased operative mortality [113,118].

Preoperative aortic root size has been shown to predict the need for reintervention for postoperative LVOT obstruction after single-stage repair of IAA with VSD. In a single-center study of 70 patients with IAA and VSD, 23% of patients required a reintervention for LVOT obstruction with a median time to reintervention of 1.2 years [115]. Subaortic resections were performed via a surgical approach while aortic valve stenosis was treated with aortic balloon valvuloplasty. Patients with a preoperative aortic root size <6.5 mm were at greater risk of requiring an intervention on the LVOT following their initial repair.

In one study, 15 of 49 patients with type B IAA had a coexisting anomalous right subclavian artery [122]. In some cases, the left subclavian artery may be utilized during the surgical repair. The use of an umbilical artery catheter is ideal in this setting. Central venous access is helpful for the infusion of inotropic agents and monitoring of intracardiac pressures. This can be accomplished by either percutaneous catheterization or placement of intracardiac lines by the surgeon prior to separating from CPB. Echocardiography using a pediatric TEE probe can effectively guide inotropic and fluid management, determine the adequacy of VSD closure, and assess the LVOT for any evidence of obstruction. Two intravenous catheters should be placed, as significant blood loss may occur following separation from CPB. The use of deep hypothermia places the infant at higher risk for significant bleeding after CPB; red blood cells, platelets, and cryoprecipitate should be available. In the case of the infant with DiGeorge syndrome, the use of irradiated blood is necessary to avoid graft-versus-host reactions [123].

Separation from CPB usually requires inotropic support and close monitoring of serum calcium levels. The infant with DiGeorge syndrome is prone to hypocalcemia and may benefit from a calcium infusion. Once the hemodynamics are stabilized and the bleeding is controlled, sternal closure may be attempted. Inotropic support, fluid management, and ventilation may need to be adjusted at this time. The patient should be closely monitored for pulmonary hypertension following repair and, if present, may benefit from inhaled nitric oxide. Should sternal closure result in unacceptable instability due to a reduction in cardiac output or pulmonary function, a polytetrafluoroethylene patch may be placed over the open chest for subsequent closure in 1–3 days.

### Anesthetic considerations

Intravenous access will have been established in the neonate with IAA scheduled for surgery. Induction of general anesthesia is usually accomplished with an opioid and benzodiazepine in combination with a non-depolarizing muscle relaxant. Inhaled anesthetic agents can be safely used as long as blood pressure is closely monitored and maintained. Management of ventilation following anesthetic induction and intubation is aimed toward optimizing systemic cardiac output. The use of a low inspired FiO₂ and avoidance of hyperventilation reduces pulmonary overcirculation. The use of cerebral NIRS can help to guide anesthetic management during this period.

The optimal position for placement of the arterial catheter requires careful consideration in the infant with IAA. The right subclavian artery may originate in an anomalous fashion from the descending aorta, especially in a type B IAA with associated subvalvular AS [122].

### KEY POINTS: INTERRUPTED OR HYPOPLASTIC AORTIC ARCH

- 70% are type B (L common carotid-subclavian artery; 90% VSD), 25% type A (distal to L subclavian artery; 50% VSD), 5% type C (innominate-left common carotid)
- Another important associated cardiac finding in the child with an interrupted arch includes LVOT obstruction.
- Neonates with an IAA or severely hypoplastic aortic arch are dependent on patency of the ductus arteriosus for blood flow to major abdominal organs and the lower extremities.
- IAA should be considered a chronic disease for which future interventions on the aortic arch and/or LVOT are common.
- Management of ventilation prior to CPB includes the use of a low inspired FiO₂ and avoidance of hyperventilation to increase pulmonary vascular resistance.
Shone’s anomaly

Incidence, anatomy, and natural history
Shone’s anomaly (or Shone’s complex) consists of a supravalvular mitral ring, parachute deformity of the mitral valve, subvalvular AS, and coarctation of the aorta, and was first described by Shone and colleagues in 1963. This complex of lesions causes multi-level left heart obstruction and is variable in regard to the presence and severity of each lesion [124,125]. In 30 consecutive patients with Shone’s anomaly, 73% had a supravalvular mitral ring, 87% a parachute mitral valve, 87% had subvalvular AS, and 97% had coarctation of the aorta. Additional lesions also present in these patients were a bicuspid aortic valve (61%) and a VSD (67%) [125]. The parachute mitral valve describes a mitral valve deformity where two mitral valve leaflets are supported by only one papillary muscle and the chordae are usually shortened and thickened. Because the mitral leaflets are pulled together in proximity, the mitral valve can become stenotic. The supravalvular ring is a ridge of connective tissue arranged circumferentially on the atrial side of the mitral leaflets. Although this ring does not cause severe obstruction in the majority of cases, fibrous tissue can obtrude into the mitral inflow tract, causing obstruction. Although not classically considered part of Shone’s anomaly, “typical” congenital mitral stenosis with a small annular size has been noted in 25–50% of patients with Shone’s anomaly in two published series [126,127]. Subvalvular AS is caused by either a discrete membranous thickening in the outflow tract or a more complex long-segment “tunnel” stenosis. The coarctation is usually located in the descending aorta in proximity to the left subclavian artery.

Cor triatriatum must also be considered in the setting of left-sided obstructive disease. The anomaly is characterized by the pulmonary venous return entering an accessory left-sided chamber that connects with the left atrium through a slender passageway. The left atrial appendage and fossa ovalis are always distal to the obstructing membrane. In contrast, a supramitral stenosing ring, when present as part of Shone’s complex, leaves the left atrial appendage in connection with the upper portion of the left atrium and proximal to the stenosing formation [128].

The natural history of Shone’s anomaly is highly variable and dependent on the severity of the left-sided obstructive lesions and the degree to which the obstructive lesions can be relieved. In particular, the degree of involvement of the left ventricular inflow tract is the major factor, which determines long-term outcome. In a recent study of 45 children with Shone’s anomaly, the cumulative survival rate was 70% at 15 years following mitral valve repair, and risk factors for reoperation and mortality included the severity and type of mitral valve abnormalities, LVOT lesions, and pulmonary hypertension [129].

Pathophysiology
Patient symptoms depend on the anatomic location of the most critical areas of obstruction. As many as two-thirds of patients with Shone’s anomaly may present in the neonatal period with an aortic coarctation [127]. Assessment of the hemodynamic significance of lesions causing obstruction of the mitral valve or subaortic region can be very challenging in the context of a ductal-dependent systemic circulation. Subsequent to the repair of aortic coarctation, these infants are followed closely for signs of congestive heart failure often related to mitral valve abnormalities. Subvalvular AS is rarely significant in the neonatal period but can rapidly progress during infancy [34]. Those patients with a high degree of subvalvular AS will develop left ventricular hypertrophy.

Echocardiography and cardiac catheterization with angiography are the primary diagnostic modalities for detecting and defining the extent of the Shone’s anomaly [130]. The presence of markedly elevated pulmonary vascular resistance at cardiac catheterization increases perioperative risk and worsens long-term outcome. It is extremely important to be aware of all levels of obstruction, because the intraoperative repair of one obstruction may often reveal other less critical stenoses that continue to impede blood flow. Failure to recognize all levels of obstruction leads to increased perioperative risk for the patient.

Surgical and transcatheter approaches and outcomes
The intracardiac surgical repair generally consists of resection of the supravalvular mitral ring, fenestration of the mitral valve tensor apparatus, repair or replacement of the mitral valve, and resection of any encroaching muscular tissue in the LVOT. When aortic arch obstruction is present, surgical repair of this lesion may be necessary during the neonatal period. Early mitral valve repair is advocated whenever possible, allowing for continued annular growth and avoidance of anticoagulation, and should occur before pulmonary hypertension develops [127]. When subvalvular AS is caused by a discrete membranous lesion, resection is performed through a transaortic approach and accompanied by ventricular septal myectomy, which is felt to reduce the incidence of recurrence [131]. A long-segment “tunnel” type of subvalvular AS is commonly corrected with an aortoven-triculoplasty (Konno procedure). Depending on the degree of aortic valvular obstruction, a Ross–Konno operation may be necessary to optimally relieve the obstruction [132,133]. Intraoperative TEE is important for anatomic assessment before CPB and then following surgical repair. Surgical and long-term outcomes for Shone’s anomaly depend on the age of presentation, severity of mitral valve disease, need for multiple surgical procedures, and presence of pulmonary hypertension [2,125–127]. Despite an initially satisfactory mitral valve repair, approximately
one-half of children with Shone’s anomaly will require a subsequent repair or mitral valve replacement [129].

Diagnostic cardiac catheterization is often indicated in the patient with Shone’s anomaly to better assess the relative hemodynamic significance of multi-level left-sided obstructive lesions and the degree of pulmonary hypertension. Catheter-based interventions may also be indicated to address primary or recurrent aortic arch obstruction.

**Anesthetic considerations**
The medical management of patients with Shone’s complex depends on the location of the most critical stenosis. Neonates with coarctation of the aorta will require prostaglandins to maintain patency of the ductus arteriosus and appropriate ventilatory strategies aimed at reducing pulmonary overcirculation. Children with dynamic LVOT obstruction may require β-blockers to improve intracavitary laminar blood flow. Congestive heart failure is usually treated with diuretics and may require inotropic support, while pulmonary hypertension before or after surgery may require a phosphodiesterase inhibitor (such as milrinone) and nitric oxide [134,135].

The anesthetic management of the patient with Shone’s anomaly requires an appreciation of all levels of stenosis and knowledge of the location of the dominant lesion. A patient with predominantly mitral stenosis requires sufficient preload to maintain left atrial pressure, and a normal to slow heart rate to optimize ventricular filling during diastole. In the patient primarily suffering from subvalvular AS and left ventricular hypertrophy, arterial pressure needs to be maintained for optimal myocardial perfusion. An anesthetic plan carefully tailored to meet these hemodynamic goals is vital for optimal outcome.

<table>
<thead>
<tr>
<th>KEY POINTS: SHONE’S ANOMALY</th>
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<tr>
<td>• Shone’s anomaly consists of multiple left-sided obstructive lesions, including a supravalvular mitral ring, parachute deformity of the mitral valve, subaortic stenosis, and coarctation of the aorta.</td>
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<tr>
<td>• The presence of multiple levels of obstruction can make assessment of the degree of obstruction at each level extremely challenging.</td>
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<tr>
<td>• Important principles of anesthetic management include maintaining sufficient preload, a normal to slow heart rate to optimize ventricular filling, and maintaining arterial blood pressure to assure optimal myocardial perfusion.</td>
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**Mitral stenosis**

**Incidence, anatomy, and natural history**
Mitral stenosis is most often observed as a component of a complex left-sided malformation syndrome, i.e., Shone’s anomaly. Isolated congenital mitral valve stenosis is a rare lesion, occurring in well less than 1% of infants with CHD and a normal-sized left ventricle [136]. The anatomical complexity of the mitral valve and its supporting apparatus, the papillary muscles and chordae tendineae, have led to several complicated schemata to describe abnormalities of the mitral valve [136–138]. One functional classification of mitral stenosis anatomy divides this lesion into type A, with a normal papillary muscle, which includes commissural fusion, a valvular or supravalvular ring, or an obstructive left superior vena cava, and type B, which consists of an abnormal papillary muscle producing a parachute, or a hammock mitral valve. [138]. The natural history of mitral valve stenosis is dependent on the severity of the stenosis and the feasibility of repair or replacement.

**Pathophysiology**
Depending on the degree of mitral stenosis, a progressive elevation in left atrial pressure can lead to pulmonary venous and then pulmonary arterial hypertension. This can result in interstitial pulmonary edema, “cardiac asthma,” frequent respiratory infections, tachypnea, poor feeding and poor growth. Significant pulmonary hypertension will be accompanied by elevated right ventricular pressures, right ventricular hypertrophy, and potentially diminished function. Left-sided cardiac output will be restricted by diminution of blood flow into the left ventricle. A resultant tachycardia shortens diastolic filling time and can severely depress systemic cardiac output. Hypovolemia reduces left ventricular end-diastolic volume and pressure, worsening the functional mitral stenosis. In patients with elevated pulmonary artery pressure and resistance, maneuvers to reduce PVR may paradoxically worsen the obstructive pulmonary symptoms by promoting increased pulmonary blood flow in the face of a fixed downstream obstruction. A frequently dilated left atrium predisposes to atrial arrhythmias such as atrial flutter, atrial fibrillation, or atrial tachycardia.

Anatomical diagnosis of mitral stenosis is often based solely on echocardiographic findings. Three-dimensional echocardiography is particularly useful in defining the morphological complexity of the diseased mitral valve and its use is increasingly widespread [139,140]. Decisions about intervening are made on the basis of increasing clinical symptomatology, such as frequent respiratory infections and failure to thrive despite optimal medical management.

**Surgical and transcatheter approaches and outcomes**
When surgery is indicated, most congenital heart surgeons adopt a conservative approach, repairing the stenotic valve whenever possible [141]. There are a number of techniques employed, including resection of a supravalvular ring,
commissurotomy, division or reconstruction of the papillary muscles, and reconstruction of the chordae tendineae [138,141]. The main goal of surgery is to reduce the mitral stenosis without producing mitral regurgitation; the surgeon will often perform a test of the repair with the aorta cross-clamped by rapidly instilling saline solution through the repaired valve to produce a normal end-diastolic volume. Retention of this volume in the left ventricle signifies lack of significant mitral regurgitation. After separation from bypass, TEE is critical in assessing the adequacy of repair and the need for returning on bypass to improve the surgical result. Because of the potential morbidity from anticoagulation and the need for future replacement as a child grows, mitral valve replacement may be performed as a last resort in young children, when attempts at repair have failed. However, when a mitral valve repair cannot be successfully performed in these patients, a supra-annular mitral valve replacement may be necessary in infants because of the small size of the annulus. Surgical outcomes are dependent on the specific abnormality and the feasibility of repair. The need for mitral valve replacement increases the risk of both short- and long-term complications. In some cases, interventional catheter approaches have therefore been successfully used to dilate a stenotic mitral valve [142].

**Anesthetic considerations**

Hemodynamic goals in mitral stenosis include maintaining a low-normal heart rate to enhance diastolic filling time for the left ventricle, and maintaining preload to minimize the functional stenosis across the valve. Preserving ventricular contractility and afterload are important goals of any technique. Maintaining normal sinus rhythm is critical, so prompt recognition and treatment of atrial dysrhythmias are important. With severe mitral stenosis, the patient will have significant pulmonary hypertension and care must be taken not to induce a pulmonary hypertensive crisis, e.g., due to a large catecholamine surge secondary to inadequate anesthetic depth. On the other hand, acutely lowering PVR with excessive FiO₂ and hyperventilation will promote excessive pulmonary blood flow, often leading to worsening pulmonary function due to the fixed downstream obstruction at the level of the mitral valve.

During surgical repair, the left side of the heart will be necessary be opened, and there is the potential for retention of significant air in the heart during weaning from bypass. Accordingly, prolonged cardiac de-airing maneuvers, assisted by TEE, may be required. Some surgeons will insufflate CO₂ into the surgical field to improve the dissolution of any gas retained in the left side of the heart [143].

After bypass, a left atrial and possibly a pulmonary artery catheter may be placed by the surgeon. It is important to realize that pulmonary artery pressures may not be immediately reduced, and treatment with adequate depth of anesthesia and analgesia, milrinone, nitric oxide, high FiO₂, and mild hyperventilation may be required for hours or days. Left atrial pressure should decrease with successful mitral valve repair in the face of normal left ventricular function. TEE is crucial to assess the immediate results of the surgical repair.

**Cor triatriatum**

Cor triatriatum is a rare anomaly seen in about 0.1% of patients with CHD, consisting of a membrane or diaphragm in the left atrium, functionally dividing it into two chambers, where the pulmonary veins enter superior to the membrane [144]. Blood flows from the upper to the lower left atrial chamber through one or more orifices, and the patient’s symptoms and presentation depend on the degree of restriction of blood flow through these orifices, and can range from completely asymptomatic to severely restricted blood flow. This may result in severe left atrial hypertension, pulmonary venous and arterial hypertension, and low cardiac output, similar to that seen in severe mitral stenosis. Pulmonary symptoms such as wheezing are prominent and may be the only presenting complaint [145]. Most patients present in the first year of life, and 24–80% have associated cardiac anomalies such as anomalous pulmonary venous drainage, left superior vena cava, or HLHS. The surgical approach consists of resecting the membrane in the left atrium and repairing associated defects. Anesthetic considerations are identical to those for the patient with mitral stenosis.

**KEY POINTS: MITRAL STENOSIS/COR TRIATRIATUM**

- Hemodynamic goals include slow-normal heart rate, and maintenance of normal sinus rhythm and adequate preload and afterload.
- Severe obstruction from these lesions can result in significant left atrial hypertension, and pulmonary venous and arterial hypertension, which may need to be managed with inhaled nitric oxide after surgical repair.
- In the face of severe obstruction pre-bypass, nitric oxide and other maneuvers to decrease PVR can worsen the problems because they do not address the anatomic obstruction.

**Selected references**

A full reference list for this chapter is available at: [http://www.wiley.com/go/andropoulos/congenitalheart](http://www.wiley.com/go/andropoulos/congenitalheart)


CHAPTER 23

Anesthesia for Right-sided Obstructive Lesions

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**Introduction**

Right-sided obstructive congenital heart disease (CHD) encompasses a set of heart defects that can present with a wide range of clinical signs and symptoms. Some minimally affected teenagers and adults present with only vague complaints of exercise intolerance or fatigue. At the other extreme, right-sided obstructive CHD can be immediately apparent in the neonate who manifests severe cyanosis or congestive heart failure (CHF). All lesions of this category have the potential for right-to-left shunting of blood flow. The severity of the disease depends upon the degree of structural malformation of the heart and great vessels.

Congenital malformations that impede blood flow through the right heart can occur at a single critical anatomical area or a combination of areas. These include the right atrioventricular (AV) valve, the outflow tract of the right ventricle (RV), the pulmonary valve (PV), and the main pulmonary artery (MPA) and/or branch pulmonary arteries (BPAs). Commonly, congenital malformations affect several of these critical areas simultaneously, such as in the tetralogy of Fallot (TOF). Malformations can occur directly as a result of aberrant movement of tissues during development, or indirectly as a result of impaired flow hemodynamics due to malaligned structural anatomy. Often the resultant congenital heart deformity is a combination of both processes.

Patients with obstructive right-sided congenital heart anomalies can present in the neonatal period with either cyanosis or CHF. Right-sided lesions, which have potential for right-to-left shunting, can produce cyanosis, such as with right-to-left shunt through an atrial septal defect (ASD) or patent foramen ovale (PFO) in severe Ebstein’s anomaly (EA) or through a ventricular septal defect (VSD) in TOF. The shunt direction can vary, becoming right-to-left as right-sided pressures exceed those in the comparable left-sided chamber, providing a “pop-off” mechanism for right-sided obstructive hypertension. Neonates with restrictive right-to-left communications or...
without anatomical potential for shunt develop congestive right heart failure. Infants with obstructive right-sided lesions such as critical pulmonary stenosis (PS) or pulmonary atresia (PA) can be ductal-dependent, achieving pulmonary flow either in part or entirely from a patent ductus arteriosus (PDA). Unless patency is maintained by exogenous prostaglandin E$_1$ (PGE$_1$), increasing cyanosis can occur when the ductus arteriosus begins to close shortly after birth.

The physiology of right-sided obstructive defects and the changes that occur with surgical intervention in the context of perioperative anesthetic care and planning for such patients are described in this chapter for:

- EA
- TOF
- PS with intact ventricular septum (PS/IVS)
- PA with intact ventricular septum (PA/IVS)
- PA and VSD with major aortopulmonary collateral arteries (MAPCAs).

Other right-sided obstructions such as those that result in a single functional ventricle (e.g., tricuspid atresia) are covered elsewhere in this book.

**Ebstein’s anomaly**

**Incidence, anatomy, and natural history**

Ebstein’s anomaly is by far the most common congenital malformation of the tricuspid valve (TV). The earliest description of TV malformation was by Ebstein in 1866 [1]. EA is present in only about 0.3–0.7% of patients with CHD and occurs in approximately 1 in 20,000 live births [2]. Other tricuspid anomalies such as TV stenosis, TV regurgitation (TR), and various malformations of leaflets, chordae tendineae, and papillary muscles are much less common [3].

Ebstein’s anomaly consists of:

- A downward displacement of septal and posterior leaflet attachments at the junction of the inlet and trabecular portions of the RV
- An “atrialized” portion of the RV between the tricuspid annulus and the attachment of the posterior and septal leaflets
- A malformed RV chamber.

The dysplastic characteristics of the anomaly are quite variable in functional severity, leading to a wide range of clinical presentations from infancy to adulthood [4] (Figure 23.1).

The position, size, and shape of the posterior and septal leaflets are inconsistent in EA. Posterior and septal leaflets can insert at varying distances below the AV annulus or, in one-third of patients, can be adherent to the ventricular wall rather than being displaced. Shortened chordae often attach to deformed papillary muscles. Over one-third of EA hearts have an ASD, while most of the remaining two-thirds contain a PFO. The anterior leaflet is attached at the AV annulus superior to the other leaflets, but it is always abnormal. Often it is large and redundant, shaped like a sail, with abnormal attachments to the border of the inlet and trabecular portions of the RV. The anterior leaflet and/or the chordae can act as a barrier to blood flow from the atrium/atrialized RV to the trabecular RV. The aperture between the atrialized and trabecular portions of the RV can be restricted to slits or perforations in the anterior leaflet. As a result of the distally displaced valves, the trabecular portion of the RV is often very small, lacking an inlet chamber. The walls of the RV can be normal or thin with impaired contractile function [2,3].

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Figure 23.1  (A) Normal proximal tricuspid attachments at the atrioventricular junction (circle dotted line) and the direction of the hinge line in Ebstein’s malformation (square dotted line). The displacement of the orifice of the valve is rotational (flat arrow). ARV, atrialized right ventricle; RA, right atrium; TRV, true right ventricle. (B) The location of the functional orifice of the abnormal valve (black ovals) as observed in the series of hearts examined by Schreiber et al. [5]. CS, coronary sinus; IVC, inferior vena cava; SVC, superior vena cava. (Source: Dearani et al. [4]. Reproduced with permission of Cambridge University Press.)
The RV wall above the line of insertion of the distally displaced functions as part of the right atrium (RA), but is anatomically ventricular. This inlet portion of the RV is often thin and dilated. Although it is exposed to atrial pressures, this atrialized RV manifests electrical conduction of an abnormal ventricular pattern. In some cases, the wall of the inlet portion is so thin that it moves paradoxically during ventricular systole, dilating with RA contraction. The RA is dilated, sometimes massively.

Left ventricular geometry can be compromised by the abnormal position of the interventricular septum, resulting in a small left ventricle (LV) chamber. In addition, mitral valve prolapse can occur because the chordae tendineae of the normally situated mitral valve leaflets are altered in shape and size by the LV distortion [6].

Prenatally, severe forms of EA result in hydrops fetalis and grossly enlarged heart that induces pulmonary hypoplasia. The diagnosis is most commonly made with prenatal ultrasound screening. Depending on the degree of deformity, neonates can be asymptomatic or present with varying degrees of cyanosis and CHF that can be fatal in some instances. Cyanotic infants will not survive long without intervention. Beyond the neonatal period, affected infants and young children can continue to be asymptomatic with milder lesions or develop progressively worsening CHF with more apically displaced TVs. Older children and young adults have survived until late diagnosis due to milder forms of the anomaly with lesser hemodynamic impairments. Unless the foramen ovale is not patent, there is little exercise intolerance. Ultimately, CHF might develop from long-term effects of TR and, when it does, it is often a harbinger of death within a few years. For cyanotic children and young adults, the severity of the cyanosis correlates with a worsening prognosis. Without surgical intervention, death from EA that presents in late childhood, adolescence, or young adulthood is usually secondary to CHF in the second or third decades of life. Still, as many as 20% of these less-severely affected individuals, some of whom may be asymptomatic, may die of atrial and ventricular arrhythmias, sometimes as a sudden death event. Other late fatal events include paradoxical emboli, abscesses, and rarely infective endocarditis [7].

Pathophysiology
The effects of TV dysfunction ultimately determine the manifestation of EA in the developing heart, as TR can impair adequate development of other portions of the right heart. In utero, severe TR might result in such diminished forward flow through the RV that right ventricular outflow tract obstruction (RVOTO) and PS or even PA occurs. The volume load on the RV can create a grossly dilated RV that impairs LV function. The massive TR can produce a huge, ballooned RA. The symptomatic neonate with EA generally shows rapid improvement of hemodynamics in the postnatal period due to gradual reduction of pulmonary vascular resistance (PVR) [8].

The neonatal clinical presentation of EA varies greatly depending upon the extent of the downward displacement of the TV leaflets and the consequences of severe TR to the rest of the heart. If the ASD is unrestrictive, the infant will be cyanotic until PVR falls in the postnatal period to near adult levels, but cardiac output (CO) might be sufficient. A restrictive ASD can result in low CO due to impairment of LV function due to malposition and paradoxical motion of the interventricular septum. Non-compaction of the LV, a phenomenon of arrested morphologic development of the LV that results in large trabeculations and intratrabecular recesses and poor function, is sometimes associated with EA, causing systolic and diastolic dysfunction, ventricular arrhythmias, and an increased risk for systemic emboli [9].

Ebstein’s anomaly is often complicated by life-threatening arrhythmias that further reduce function in an anatomically impaired heart. Atrial flutter, atrial fibrillation, and paroxysmal supraventricular tachycardia occur in 25–30% of patients, and other electrophysiologic abnormalities are also common [10] (Box 23.1). To make matters worse, accessory pathways are more difficult to ablate with EA than with hearts with normal anatomy, and the recurrence rate post-ablation is higher [9].

**Box 23.1:** Major electrophysiologic abnormalities in Ebstein’s Anomaly
- Intra-atrial conduction disturbance: right atrial P-wave abnormalities, PR interval prolongation
- Atrioventricular nodal conduction: PR interval prolongation
- Infranodal conduction
  - Intra-His or infra-His conduction abnormalities
  - Right bundle branch block
  - Bizarre second QRS attached to preceding normal QRS
- Type B Wolff–Parkinson–White pre-excitation
- Supraventricular tachycardia
- Atrial fibrillation or flutter
- Arrhythmogenic atrialized right ventricle
- Deep Q waves in leads V1–4 and in inferior leads

Surgical intervention is not necessary in the infant and child unless tricuspid incompetence results in progressive right heart failure, the RV pumping chamber is inadequate, or there is other right-sided obstruction concurrent with the Ebstein TV. Moderate CHF due to TR can be managed with digoxin in combination with diuretic therapy. Dysrhythmias may be medically controlled or eliminated with catheter ablation in some instances. Early surgical intervention is sometimes necessary to avoid further deterioration of the TV and RV and to improve long-term outcome [11].

### Surgical and transcatheter approaches and outcomes
The natural history of the disease varies with its severity, and accordingly, the management of EA is based on its severity and the age at which surgical intervention is necessary. The size of the trabecular portion of the RV
usually determines whether the patient is eligible for a two-ventricle, one-and-a-half-ventricle, or single-ventricle repair/palliation. For the neonate, further consideration is given to the degree of RVOTO and the transitional decline of PVR from prenatal to near adult levels. Cardiac transplantation is generally reserved for the most severely afflicted infants, and perhaps those with significant LV dysfunction [8].

Although Hunter and Lillehei proposed an early repair of the EA TV in 1958 based on pathological specimens [12], the first successful repair was performed in 1963 as valvuloplasty techniques were rapidly evolving [13]. Modifications of this first technique by Danielson et al. [14] and others from 1972 onward have led to survival of many of patients who benefited from improvements in valvuloplasty, reduction atrioplasty, and ablation of accessory conduction pathways. Important developments in the repair of EA of the TV over the past 25 years have included improvements such as:

- **Valvuloplasty techniques:**
  - Enhanced TV coaptation, reducing TR
  - Relocation of the TV to the true annulus, and improved remodeling of the relocated TV annulus
  - Improved central TV flow with less restriction
  - Stabilization of the TV annulus with rings and partial rings

- **Plication, and improved plication techniques applied to the atrialized RV in order to improve RV functional morphology.**

- **Improvements in ablation of accessory conduction pathways.**

First developed in 1989, cone reconstruction of the TV has evolved as a preferred technique for repair of the Ebstein’s anomalous TV. Advantages of this technique include improved TV leaflet coaptation and centralized flow [15–17] (Figures 23.2–23.5). Other techniques have redirected the large anterior leaflet in order to have it approximate the ventricular septum or the adjacent small, malformed septal leaflet, plicated the tricuspid annulus and the atrialized RV. The result is a TV comprising either a large single anterior leaflet (monoleaflet valve) or a bicuspid valve with one very large leaflet (anterior) and one very small leaflet (septal). The cone technique maximizes valvular tissue by delaminating inferior and septal leaflet tissue and a portion of the anterior leaflet (from the point that it deviates from the true tricuspid annulus) from the myocardium by incising muscular and fibrous attachments while maintaining chordal attachments to the leading edges of the leaflets. Sometimes in the absence of true chordal attachments, a linear attachment can be fashioned into “neochordae” by creating surgical fenestrations. Using leaflet tissue maximized by surgical delamination, the inferior and septal leaflets are combined into a larger leaflet that approximates the partially delaminated anterior leaflet. Longitudinal plication of the atrialized RV can be completed from the endocardial side of the myocardium. The true tricuspid annulus is plicated as necessary followed by reattachment of the inferior/septal leaflet and the surgically separated portion of the anterior leaflet at the level of the true tricuspid annulus [15] (Figures 23.2 and 23.3). Because the tricuspid annulus is often dilated, flexible annuloplasty rings can be added for stability. For children, a partial ring can provide...
some annular support and allow for growth. As leaflet size varies greatly in Ebstein’s malformation, augmentation of leaflet tissue with patch material is sometimes helpful to improve leaflet coaptation and central flow, and/or to avoid post-valvuloplasty TV stenosis [17]. The cone technique appears to improve coaptation of the surgically revised leaflets, reducing TR and allowing for more centralized tricuspid flow.

Dysrhythmias are often problematic after surgical repair of EA, and temporary pacing wires placed on the RA and RV during surgery are useful in some patients for monitoring of rhythm postoperatively or pacing. For teenaged and adult patients with preoperative dysrhythmias, intermediate follow-up post-repair indicates substantial reduction of dysrhythmia in survivors who did not require placement of pacemakers [18].

Risks with the cone technique include impairment of right coronary artery flow due to distortion caused by plication of the tricuspid annulus or sutures to the inferior RV wall, inadvertent creation of tricuspid stenosis, suture dehiscence, and third-degree AV block if sutures are placed too close to the AV node. Recent cone reconstruction for the neonate has been successful in a few reports [19,20]. It has the same advantages for valve function, but precludes the use of an annuloplasty ring.

Long-term results for the cone reconstruction technique are limited. In a longitudinal study [21] of 52 consecutive patients aged 0.25–49 years (mean 18.5 ± 13.8 years) receiving operations over a 13-year period, 97.9% survived to hospital discharge. There were two late deaths: one from infectious TV endocarditis after dental work and another 7 years after surgery due to RV dysfunction and ventricular arrhythmias (overall survival 94.2%). Reoperation for repeat tricuspid valvuloplasty occurred in four patients 3–10 years later: two for significant tricuspid regurgitation, one for surgical dehiscence of the septal portion, and one for unknown valve failure. Atrial arrhythmias occurred in three patients; one was managed with ablation and two with medical management. Significant long-term improvement was seen for reduction in TR, improved functional RV area, reduced cardiothoracic ratio, and New York Functional Class data for 47 patients over 57.44 ± 45.14 months.

For Ebstein TV repairs other than the cone technique, long-term outcome analyses generally include a mix of adult and pediatric patients with few or no neonates and review patients over many years who have had many variations of TV repair. A large review of 539 patients at the Mayo Clinic [22] included an analysis of 44 pediatric patients having TV repair or 105 having replacement who were <12 years old between 1972 and 2006. While 1-year survival was well above 90% for both groups, survival rates for 5, 10, and 20 years without need for late operation were 39, 27, and 20%, respectively, for TV repair and 61, 23, and 7%, respectively, for TV replacement. Those undergoing TV replacement were more likely to have had surgery later in the study period, worse abnormalities...
of the TV, earlier age at diagnosis, worse LV systolic function, hypoplastic or stenotic pulmonary arteries, and post-repair RV enlargement, and were less likely to have had a concurrent atrialized RV plication.

In a study of 52 infants and children 5 months to 12 years old undergoing repair with variations of the Danielson technique [4,14] between 1974 and 2003, estimated survival rates at 5, 10 and 15 years were 92%, 90%, and 89%, respectively, and rates of freedom from reoperation for recurrent TR were 91%, 80%, and 68%, respectively [23]. A more recent study of 32 neonates and infants undergoing TV repair with variations of the Danielson technique (29 with biventricular repairs) between 1994 and 2010 found an early survival rate of 78% with an estimated 15-year survival rate of 74% ± 8%. For the 23 neonates of this group, PA was associated with a lower estimated 15-year survival of 40% ± 15%, compared with 79% ± 13% without PA [24].

In a recent short-term outcome comparison study [16] between the cone technique and conventional TV repair or replacement for Ebstein’s TV malformation, 19 patients with a cone reconstruction showed an 85% reduction in TR at discharge, compared with a 56% reduction for 13 patients with conventional repair (nine patients) or replacement (four patients). The 56% reduction in TR seen at discharge in the conventional group worsened on later follow-up studies, while the 85% TR reduction in the cone technique group was maintained. This study looked primarily at older pediatric patients and adults (median age 18.1 years for cone technique and 14.1 years for the conventional technique), including one infant in each group, no neonates, and a minority of patients less than 12 years of age (six out of 19 in the cone group and three out of 13 in the conventional group).

Decision-making for the type of surgical repair or palliation relies on two critical assessments: the morphology of the TV and the size of the pumping chamber of the pulmonary ventricle. In the past, some infants with adequately sized RVs have done well with an aggressive two-ventricle repair that included reconstruction of a monocuspid TV from the anterior leaflet, ventriculorraphy, reduction atrioplasty, subtotal closure of the ASD, and repair of other associated defects [25]. Severe anomalies of the Ebstein’s TV may preclude any neonatal TV repair, and suitable prosthetic valves are not available for the small neonatal TV anulus. In the early 1990s, the Starnes procedure, a combination of RV exclusion via pericardial patch closure of the TV, reduction atrioplasty ± RV plication, and modified Blalock–Taussig shunt (mBTS), was proposed for PGE1-dependent neonates with EA and physiologic PA, converting the cardiac physiology effectively to that of the single-ventricle system [26]. There have been many reported modifications to this procedure since that time, but the basic elements include placing a fenestrated patch over the TV orifice (to allow RV decompression from filling via the thebesian veins), creating a non-restrictive ASD, and providing for pulmonary blood flow (PBF) with an aortopulmonary shunt [9]. Sano et al. [27] have taken this concept further with the RV exclusion operation that also includes excision of the RV free wall with subsequent primary closure or closure with a polytetrafluoroethylene (PTFE) patch, removing much of the potentially arrhythmogenic RV that could impair LV function. Survival for the most severe neonatal forms of EA treated with aggressive neonatal surgery has improved, but is still much lower than for other complex congenital heart lesions. Two large single-center series report hospital survival rates of 70% and 73% [25,28].

Patients with a severely hypoplastic or poorly functioning RV might ultimately require a single-ventricle palliation with cavopulmonary anastomosis or Fontan circulation. However, there are instances when a hypoplastic or small RV is still capable of ejecting partial CO to the pulmonary arteries. These patients might benefit from a one-and-a-half-ventricle repair, allowing the diminutive RV to pump part of the systemic venous return to the lungs. The venous drainage of the upper body returns by passive flow via a bi-directional cavopulmonary connection (BCPC) to the pulmonary circulation, and ranges from one-third to one-half of the systemic venous return. In brief, the one-and-a-half-ventricle palliation includes valvuloplasty, possible repair of the ASD, and creation of a BCPC. A small ASD can be left if there is an anticipated need for a “pop-off” for systemic venous return to the “half” pulmonary ventricle. The pulmonary arteries must be of adequate size, and PVR must be low for successful implementation.

There are advantages to utilizing a semifunctional pulmonary ventricle. Preservation of some pulsatile flow to the MPA might reduce the risk of development of MAPCAs. Also, a hypoplastic pulmonary ventricle might be able to respond to increased demand by increasing CO beyond what might result with a Fontan circulation [29]. Van Arsdell et al. [30] have proposed that the one-and-a-half-ventricle palliation might be of benefit to the patients with EA who have a partial RVOTO due to billowing of the anterior leaflet. For infants and young children with severe EA and post-cone reconstruction TV stenosis, the one-and-a-half-ventricle palliation can reduce RV preload to accommodate a smaller TV opening while enhancing LV preload and maintaining biventricular oxygen saturation by closing any ASD or PFO [31].

Reported mortality with the one-and-a-half-ventricle palliation for all lesions (including EA) is variable between 0% and 12% [32,33]. Long-term outcomes have not been compared with the Fontan procedure, but the one-and-a-half-ventricle palliation seems not to have the short- and intermediate-term complications of cyanosis, chronic atrial dysrhythmias, and protein-losing enteropathies associated with the Fontan physiology [32,33]. However, an increase in perioperative effusions and chylothorax has been found. Other complications have included chronically increased superior vena cava (SVC) pressure, early-morning periorbital edema, and one instance of a SVC aneurysm. Another instance is reported of development of pulmonary arteriovenous fistulas with
a one-and-a-half-ventricle palliation in combination with the classic Glenn procedure [32]. Valvuloplasty is preferred in infants and young children due to the need to upsize valves as the child grows. The teenager who has nearly reached adult size might do better with a prosthetic valve, as the native valve might have incurred much damage due to abnormal dynamics over time. Children who have had previous TV repair of EA with techniques employed prior to the cone reconstruction may benefit from re-repair using the cone technique [17]. Later re-repair with a cone reconstruction is facilitated if the leaflets were not delaminated at a previous repair, allowing for more leaflet tissue to be employed.

**Anesthetic considerations**

**Preoperative**

Given the variability in presentation, the pre-anesthetic evaluation of the infant or child with EA must include an assessment of the severity of the disease. Specifically, the patient is evaluated for symptoms of fatigue, dyspnea, and, if there are signs of cyanotic episodes, whether these are becoming more frequent or severe. One can assess exercise tolerance for an individual child by asking about the child’s ability to play with the same vigor as the child’s healthy peers. For an infant, one can focus questions for the caretakers on typical infant activities and growth; poor feeding ability, failure to thrive, and/or signs of dyspnea, irritability, cyanosis, or diaphoresis are indicative of a poorly functioning heart. A history of syncope, chest pain, and palpitations suggests dysrhythmia in the older child.

With EA, physical examination might be notable for triple or quadruple heart sounds, often with a soft, high-pitched systolic murmur. A soft, scratchy mid-diastolic murmur heard best at the left sternal border and apex might be present. The second heart sound is widely split with little respiratory variation due to delayed emptying of the RV. With failure, the child can be diaphoretic, tachypneic, and irritable with rales present on chest auscultation and hepatomegaly on abdominal palpation. The chest roentgenogram can reveal moderate to severe cardiomegaly with a large RA and diminished pulmonary vascular markings. The heart often has a globular shape. Electrocardiogram (ECG) usually suggests RA hypertrophy, an increased PR interval, and complete or incomplete right bundle branch block. Interestingly, the pre-excitation patterns of Wolff–Parkinson–White syndrome are seen in 10–15% of individuals. Two-dimensional echocardiography is usually diagnostic, revealing a large tricuspid orifice complete with apical displacement of the septal leaflet of the TV. Cardiac catheterization is seldom indicated and can be complicated by induction of tachyarrhythmias. Magnetic resonance imaging (MRI) is increasingly being used to measure displacement of the TV leaflets and to estimate the functional size of the RV [33].

The cyanotic neonate benefits from a reduction in PVR. Prevention of atelectasis with adequate tidal volumes while minimizing airway pressure in the intubated infant is beneficial. Nitric oxide might be useful for encouraging PBF in the neonate with marginal heart function and could help to distinguish between functional and anatomic obstructions to PBF. Often, PGE$_1$ is necessary in the early neonatal period to augment pulmonary arterial blood flow by maintaining the PDA. However a large PDA can cause high output cardiac failure with what is known as a “circular shunt.” In this circumstance, generous blood flow from the aorta flows through the PDA into the left pulmonary artery (LPA), but follows the course of least resistance retrograde sequentially through the MPA, PV, RV, RA, ASD or PFO, LA, LV, and again into the aorta with minimal perfusion of the pulmonary capillary bed (Figure 23.6). Discontinuation of the PGE$_1$ reduces this shunt by allowing the PDA to become smaller, increasing afterload and reducing high output failure [9].

Midazolam, given either orally (0.5–0.75 mg/kg up to 15–20 mg) or intravenously (0.1–0.15 mg/kg up to 2–4 mg), is an effective anxiolytic for most patients, including infants who manifest stranger anxiety (approximately 9 months of age and older). A relaxed infant or child can

![Figure 23.6](image-url)
facilitate a smooth induction by avoiding decreased PBF that can occur with crying and breath holding.

**Intraoperative**

For infants and children with mild to moderate disease, an inhalational induction with nitrous oxide and sevoflurane can provide a smooth transition to the anesthetized state. Lowered CO or small right-to-left shunt at the atrial level can slow an inhalational induction. Alternatively, intravenous (IV) induction with ketamine (1–4 mg/kg) or propofol (1–2 mg/kg) can provide reasonable induction hemodynamics. For patients with moderate to severe TV pathology, IV induction with glycopyrrolate and ketamine (1–4 mg/kg) or etomidate (0.2–0.3 mg/kg) allows stable hemodynamics in most instances without excessive myocardial depression or reduced afterload. As EA patients are dependent upon adequate preload, increases in vascular compliance due to anesthetic-induced vasodilation need to be met with IV volume replacement such as with 5% albumin or crystalloid solution. Choices of muscle relaxant depend upon the expected duration of the procedure and the need for rapid-sequence or modified rapid-sequence induction techniques. Rocuronium is an excellent choice for induction (0.6–1.2 mg/kg) and maintenance (0.1–0.2 mg/kg every 20–30 minutes) of neuromuscular blockade. When available, pancuronium, a long-acting muscle relaxant is sufficient for most cases and provides vagolysis via ganglionic blockade for a sustained rise in baseline heart rate. The maintenance technique is often opioid-based (fentanyl 10–20 μg/kg prior to cardiopulmonary bypass [CPB] and 25–50 μg/kg, total, for patients who will be mechanically ventilated immediately postoperatively) with low-dose isoflurane (e.g. 0.4%) prior to onset of CPB. Lower doses of fentanyl (15–20 μg/kg, total) and a higher minimum alveolar concentration (MAC) of a halogenated agent such as isoflurane, sevoflurane, or desflurane can be used with patients who have sufficient cardiac reserve to tolerate the myocardial depressant effects of the halogenated agents. Myocardial [34,35] and neurological [35,36] preconditioning and delayed preconditioning [37] have been demonstrated in vitro and in animal models when administered near 1 MAC prior to a significant ischemic event, and might provide a protective effect for cardiac surgery. For repeat sternotomy, plasmin-binding inhibitor antifibrinolytic drugs such as epsilon-aminocaproic acid or tranexamic acid can reduce blood loss during the pre- and post-CPB period.

Five-lead ECG with an ability to display multiple lead tracings is useful in monitoring changes in rhythm during both the pre- and post-repair periods. For the cone reconstruction, compromise of the right coronary artery during the repair might be suggested by ST elevation in leads II, III, or AVF or reciprocal depression in I or AVL. Complete heart block, sinus node dysfunction, or junctional rhythms after removal of the aortic cross-clamp might be temporary or sustained, but temporary pacing may be needed to improve hemodynamics sufficiently to separate from CPB or to maintain adequate post-CPB CO. Other than standard monitoring, near-infrared spectroscopy is useful for monitoring brain and somatic oxygenation, especially during the non-pulsatile flow of CPB. Transcranial Doppler flow velocity gives an insight into changes in cerebral blood flow within the clinical context and provides extremely sensitive detection of gas or particulate emboli entering the cerebral circulation, but can be technically difficult to maintain during surgery due to the need to keep the device precisely positioned. Intraoperative transesophageal echocardiography (TEE) allows one to check for clearance of air bubbles in the systemic heart chambers prior to cessation of CPB and to rapidly assess the function of the TV in the immediate post-CPB period.

Patients with severely dilated right hearts are at high risk for potentially lethal ventricular arrhythmias post-repair. Prior to separation from CPB, a prophylactic IV infusion of an anti-arrhythmic drug such as lidocaine (20–50 μg/kg/min) or amiodarone (3–5 mg/kg over 30 minutes, then 2 mg/kg/day, maximum 20 mg/kg/day or 2.1 g/day) can lend some protection against ventricular arrhythmias. Patients who have undergone RV plication as part of the repair are at added risk for ventricular arrhythmias. Inotropic drugs that promote forward flow in the right heart (e.g. milrinone 0.3–0.5 μg/kg/min, low-dose epinephrine 0.02–0.04 μg/kg/min, or dobutamine 5 μg/kg/min) can improve hemodynamics for hearts with pre-existing myocardial dysfunction after separating from CPB. Generous RV filling pressures might be needed to maintain adequate preload with a poorly functioning ventricle.

For those with good ventricular function and mild TR, limiting the amount of post-CPB opioid and muscle relaxant while utilizing gas anesthetics can facilitate spontaneous ventilation and extubation at the end of surgery. Once the sternum has been closed and neuromuscular blockade has diminished, spontaneous ventilation with a pressure support ventilation mode can be used. IV acetaminophen can allow for a reduced opioid requirement and less opioid-induced sedation at the time of extubation. Opioids can be titrated to respiratory rate and muscle relaxant reversed prior to extubation, such that ventilation and airway patency are adequate in the early post-anesthetic period.

**Postoperative**

At the end of surgery, patients are transported to an intensive care unit (ICU) equipped to care for the postoperative pediatric cardiac patient with continuous monitoring for rhythm and arterial blood pressure. Pain can be well controlled with opioid infusions such as morphine sulfate (20–80 μg/kg/hour, depending on the need for sedation beyond analgesia). For some patients with significant ventricular dysfunction or residual TR, it is prudent to allow a gradual emergence from opioid sedation and inotropic support in order to assess the remodeled tricuspid competency and allow more time for recovery.
of myocardial function. Midazolam (0.1–0.2 mg/kg/h) or dexmedetomidine (0.5–1 μg/kg/hour) can be added simultaneously with opioid analgesic infusion to provide sedation for patients who need longer myocardial recovery times and remain intubated and ventilated beyond the operative day.

As stated earlier, dysrhythmias are common in the immediate postoperative period after repair of EA, and can persist as a late complication of repair. Supraventricular tachycardia, junctional rhythm, or intermittent AV block can complicate recovery. Risk for ventricular arrhythmias and sudden death persists through the first postoperative month. Those patients who demonstrate perioperative ventricular tachycardia or ventricular fibrillation are likely at greatest risk [38]. Patients with intermittent AV block or junctional rhythm might benefit from temporary pacing to enhance CO in the immediate postoperative period. As myocardial edema subsides, return of functional conduction pathways might allow return of normal sinus rhythm. As previously mentioned, IV amiodarone or lidocaine might be helpful in the early postoperative period, and switching to oral amiodarone for several months might be warranted for high-risk individuals.

In the early postoperative period, echocardiography often shows poor coaptation of the TV leaflets. This finding is probably due to post-CPB dysfunction of the papillary muscle bundles (possibly of ischemic etiology) as the leaflet coaptation often improves with subsequent echocardiographic examinations.

**KEY POINTS: EBSTEIN’S ANOMALY**

- Gradually, cyanosis and PBF will improve in symptomatic neonates as PVR decreases.
- Depending on the potential for functional remodeling and relocation of the TV to the true annulus and the adequacy of RV morphology, EA may be remedied by a biventricular repair for less severe forms, or palliated with a one-and-a-half-ventricle or single-ventricle physiology for more severely affected individuals.
- Patients with extreme cardiomegaly or perioperative ventricular arrhythmias should receive prophylactic antiarrhythmic treatment, such as amiodarone.
- Patients with poorly functioning RVs are dependent upon high filling pressures to maintain adequate CO.

**Tetralogy of Fallot**

**Incidence, anatomy, and natural history**

Representing 10% of all congenital heart defects, TOF is the most common form of cyanotic heart disease. Although first described in 1671 by Niels Stensen, Etienne Fallot was the first to make a bedside diagnosis that was confirmed postmortem. Based on numerous postmortem studies, he published a comprehensive clinical and anatomical description in 1888, introducing the term “tetralogy.” Classic TOF consists of four abnormalities (the “tetrad”) [39] (Figure. 23.7):

1. A large unrestrictive VSD
2. RVOTO
3. Overriding of the aorta above the right ventricular outflow tract (RVOT)
4. RV hypertrophy.

Embryologically, TOF might result from incomplete rotation and faulty partitioning of the conotruncus during septation, resulting in the conus septum developing too far anteriorly, producing two unequal-sized vessels – a large aorta and a smaller pulmonary trunk.

The VSD is perimembranous, large (usually the same diameter as the aorta), and unrestrictive. The cardiac conduction tissue lies in close proximity to the margins of the VSD and can be damaged during repair, producing temporary or permanent heart block. Additional muscular VSDs might also be present. The aortic outflow overrides the VSD and thus has a biventricular origin, receiving a variable amount of blood from the RV depending on the degree of RVOTO. In 25% of TOF patients, the aortic arch is right-sided, with mirror image branching of the head vessels. Other associated rare vessel abnormalities include an aberrant origin of the ipsilateral subclavian artery from the descending aorta and an isolated origin of the left subclavian artery from the pulmonary artery. These abnormalities can have implications when selecting the surgical approach for the placement of palliative shunts.

Coronary abnormalities occur in 5–12% of patients with TOF. Failure to detect these preoperatively can have serious consequences for a successful outcome if they are injured in the surgical repair. The most common abnormality consists of a left anterior descending artery that originates from the right coronary artery and crosses the RVOT inferiorly. This arrangement makes it very susceptible to damage if the transannular incision is carried too far inferiorly across the RVOT. Indeed, an alternative surgical approach might be needed to relieve the subpulmonary obstruction, or alternatively an RV to MPA conduit might be required. Other coronary anomalies include a right coronary artery originating from the left coronary artery and a left coronary artery originating from the MPA. Precise definition of the coronary anatomy might be possible with echocardiography alone. If there is still uncertainty, aortic root or selective coronary angiography can be used, but it is sometimes a risky procedure in an unpalliated patient due to the danger of a severe hypercyanotic spell caused by cardiac catheter manipulations.

Other lesions that might be associated with TOF include a bicuspid PV, stenosis of the LPA, partial or total anomalous pulmonary venous return, left SVC, AV septal defect, PDA, ASD or PFO (occasionally referred to as the pentalogy of Fallot), and interrupted inferior vena cava. All of these might require modifications to the surgical repair, such as an additional venous drainage cannula in the left SVC.
Two important variants of TOF are PA/VSD and the absent PV syndrome. With PA/VSD, there is complete obstruction to RV outflow and hypoplasia of the central and peripheral pulmonary arteries. The MPA may be absent or the BPAs might be non-confluent or stenotic. Pulmonary blood supply is usually via MAPCAs. The surgical correction of this lesion is very different from that of classic TOF and is discussed later in this chapter. Absent PV syndrome is characterized by combined PV stenosis and pulmonary insufficiency (PI), which in utero produces increased pulsatile PBF, causing massive enlargement of the MPAs and BPAs. Consequently, a characteristic feature of this disorder includes airway compression and tracheobronchomalacia. These babies typically present in the neonatal period with severe respiratory distress, cyanosis, and air trapping. Tracheal intubation with high levels of positive end-expiratory pressure (PEEP) and prone positioning can be useful in maintaining the patency of the lower airways. Infants with significant lung disease often require urgent surgical intervention. The TEE probe can worsen obstruction from tracheobronchomalacia in such infants by posteriorly compressing large airways with insufficient cartilaginous support. After surgical repair, respiratory symptoms commonly persist due to the underlying intrinsic airway abnormalities, and some patients might need long-term ventilation.

In TOF, the RVOTO usually has dynamic and fixed components. The dynamic component consists of hypertrophied infundibulum and muscle bundle fibers. The hypertrophy occurs in response to the increased pressure load on the RV. Fixed components of the obstruction occur at the valvular and supravalvular levels. The PV is frequently thickened, dysplastic, and often bicuspid. There is usually some degree of pulmonary artery hypoplasia in all patients. There might also be localized narrowing of the MPAs and BPAs. Atresia or discontinuity of the main and BPAs can occur, further complicating surgical correction, as restoration of continuity or augmentation of the pulmonary arteries is required.

There is a weak association of familial inheritance of TOF. Indeed, TOF is associated with major extracardiac malformations, and might occur as part of a syndrome or association. Some examples are the VACTERL association, the CHARGE association, and Alagille syndrome, among others. Recent genetic studies have shown that TOF is associated with chromosome 22q11 deletion (“catch 22 syndrome”). This chromosomal abnormality is also responsible for DiGeorge syndrome, velocardiofacial syndrome, and conotruncal anomaly face syndrome. In one study of TOF patients, prevalence of 22q11 deletion was 13%. This deletion is considered to be the most common genetic cause of TOF-associated syndromes [40].

Autopsy and clinical series outcomes show that there is a 50% survival in uncorrected patients with TOF of 5–10 years. Survival beyond the fourth decade is very rare in untreated patients and is usually due to immense collateral blood flow or a PDA. Mortality is usually a result of hypoxemia and its hematological consequences such as endocarditis, brain abscesses and cerebrovascular accidents. Even children who are completely palliated show delayed growth and development due to the associated non-cardiac conditions. With complete repair in early infancy or childhood, over 90% of patients are expected to survive to adulthood [41].
Pathophysiology
The clinical manifestations of TOF range from extreme cyanosis at one end of the spectrum, because of profound right-to-left shunting through the VSD, to normal saturation for patients who have minimal RVOTO. The latter group is referred to as “pink tets” because of the absence of cyanosis. They might even show signs of CHF from pulmonary overcirculation. The severity of symptoms correlates primarily with the degree of RVOTO, as this determines the amount of shunting of desaturated blood into the systemic circulation. Detrimental effects of RV hypertrophy, a response to the high afterload (systemic and pulmonary), include:

- RV diastolic dysfunction requiring high filling pressures to maintain CO
- Increased difficulty for surgical repair of the VSD and resection of the RVOT muscle bundles due to a thickened, stiff ventricle
- A lessened ability to protect the hypertrophied RV during aortic cross-clamping, possibly contributing to post-operative RV dysfunction.

To limit the progression of ventricular hypertrophy, many centers now undertake surgical correction in early infancy.

With a non-restrictive VSD and equalization of RV and LV pressures, the major determinant of the degree of shunting (and hence cyanosis) is the balance of systemic vascular resistance (SVR) and PVR (at the RVOT level). A fall in SVR (hypovolemia, acidosis, hypoxia), and/or an increase in PVR (infundibular spasm) will favor right-to-left shunting and worsening cyanosis. Acute severe RVOTO occurs during a hypercyanotic or “tet spell,” and can result in syncpe or stroke. These spells can occur spontaneously, but are usually precipitated by crying, agitation, pain, defecation, injury, or fright – conditions that increase sympathetic activity and cardiac contractility, resulting in infundibular spasm. If not treated aggressively, resulting hypoxia and acidosis will further reduce SVR, leading to more right-to-left shunting. Induction of anesthesia can be particularly challenging and hazardous if IV access is unavailable. The anesthesiologist must be well prepared to treat such an episode. The goal of treatment is to use maneuvers (described later in this chapter) to reverse the amount of right-to-left shunting. “Tet spells” in patients who are conscious are usually accompanied by hyperventilation due to hypoxemia and metabolic acidosis. Older children with unrepaired TOF (rare in the current era) would adopt a squatting posture during a spell to alleviate discomfort. Squatting increases intra-abdominal pressure, thereby increasing RV preload, allowing the RVOT to open and increase PBF. Squatting also increases SVR, reducing right-to-left shunting through the VSD.

Diagnosis in the infant can be made prenatally in some instances by ultrasonography. In the neonate, a heart murmur with or without cyanosis will lead to further diagnostic evaluation. In either case, genetic screening for 22q11 deletion is often offered. Neonatal signs are variable depending on the degree of RVOTO. In newborns with critical PS and ductal-dependent PBF, the clinical presentation might be delayed until the ductus arteriosus closes. Then, the infant might develop sudden severe cyanosis during a “tet spell.”

Physical findings are not specific for TOF. Cardiac auscultation reveals a crescendo–decrescendo systolic murmur best heard at the upper left sternal border. The intensity of the murmur will decrease during a hypercyanotic spell due to diminished PBF. Clubbing is a relatively late finding in chronically cyanotic patients. The ECG usually shows RV hypertrophy and right axis deviation. The chest radiograph will show a characteristic “boot-shaped” heart, reflecting RV hypertrophy and a concave upper left heart border from a small or absent MPA. The diagnosis is confirmed by echocardiography. Other important echocardiographic information includes:

- The degree of RVOTO
- The size and location of VSDs
- Coronary anatomy
- Additional cardiac pathology such as arch-sidedness and ASD
- Biventricular function.

Surgical and transcatheter approaches and outcomes
All patients diagnosed with TOF require some form of intervention. In some centers, balloon dilation of the RVOT, with or without stent placement, is used as an alternative to a systemic artery-to-pulmonary artery shunt placement [42]. Advantages of this technique include avoiding a sternotomy or thoracotomy and distortion of the pulmonary artery anatomy from shunt placement.

The optimal timing for surgery and complete vs. staged repair are the subjects of ongoing debate, although most centers now favor total repair in early infancy, between the ages of 1 and 3 months. Other factors that influence these decisions are the institution’s capability for providing perioperative critical care to patients with complex CHD and specific anatomical features that are contraindications to complete early repair. Examples of unfavorable anatomy include the presence of coronary abnormalities, such as the left anterior descending artery arising from the right coronary artery and crossing the RVOT, the presence of multiple VSDs, and inadequate pulmonary artery anatomy. In these cases, it is reasonable to place a palliative shunt and allow the baby to grow, facilitating eventual complete repair on a larger patient. This two-stage repair subjects the baby to additional surgical procedures with attendant risks and complications:

- Potential injury to the recurrent laryngeal and phrenic nerves
- Inadequate or excessive PBF requiring shunt revision
- Potentially fatal shunt thrombosis
- Distortion of the pulmonary artery at the shunt site
- The need for a second sternotomy.
However, complete repair in the neonatal period includes not only the usual risks of performing a complex cardiac repair on a small infant and the effects of CPB on immature organ systems, but also the surgical challenges of working with smaller anatomy. Although most centers perform the repair using a transatrial–transpulmonary approach, smaller patients might need a ventriculotomy to facilitate repair.

Recently, Morales et al. [43] described a surgical paradigm of sparing the right ventricle infundibulum (Figure 23.8). The elements of this model are:

- Using a transatrial and transpulmonary approach to minimize right ventriculotomy (thus avoiding future akinesis/dilation of the RV)
- Minimizing neurologic sequelae by avoiding CPB/deep hypothermic circulatory arrest in the neonatal time period (by operating on patient > 1 month of age and/or > 4 kg or electing to place a systemic-to-pulmonary shunt off-CPB if the patient is < 1 month old and symptomatic)
- Preserving native PV function (by performing the definitive repair at ≥ 1 month of age and/or > 4 kg to allow the PV to grow and avoid a large transannular incison).

Midterm results for this approach have been promising. In a cohort of 304 patients, there was a 30-day survival of 99.7% and 1- and 7-year Kaplan–Meier survival rates of 97% and 96%, respectively. Of the 65 patients in the cohort who had been followed for 7 years, 95% had a qualitative assessment of normal RV function, with an additional 4.6% having mild RV dysfunction by echocardiogram.

**Surgical palliation**

The aim of palliation, using a systemic-to-pulmonary artery anastomosis, is to provide a stable source of PBF until complete repair can be accomplished. The “classic” Blalock–Taussig shunt (BTS), an end-to-side anastomosis of the subclavian artery to the RPA to alleviate cyanosis, was first performed in 1944. Potts and Waterston later described shunts using direct anastomosis between the aorta and PA. However, despite providing good palliation, their size was difficult to control and they were also extremely difficult to take down during subsequent complete repair and thus were largely abandoned. The most common palliative procedure in the current era is the “modified” BTS using an interposition graft between a branch of the brachiocephalic trunk (usually the subclavian artery) and the ipsilateral BPA (Figure 23.9). The advantages of the mBTS are that it:

- Preserves blood flow to the arm
- Can be placed on either side, although most are done on the right because the pulmonary anastomosis can be placed more centrally allowing easier control of the shunt during subsequent repair
- Avoids excessive PBF when appropriately sized.

An alternative procedure is to place a central shunt between the ascending aorta and the MPA using graft material. The central shunt is useful when the vascular anatomy precludes placement of an mBTS.

Some centers are now reporting stenting of the PDA in the catheterization laboratory in the early neonatal period, particularly in small or premature infants where

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**Figure 23.8** Algorithm for treatment of tetralogy of Fallot. (Source: Morales et al. [43]. Reproduced with permission of Elsevier.)
Figure 23.9 Diagram showing the various types of shunt used to increase pulmonary blood flow. The modified Blalock–Taussig shunt and the central shunts are the only shunts used in the modern era.

surgical intervention is not optimal because of small size. Requirements for this procedure are a relatively straight course of the PDA, and many authorities require a second source of PBF, i.e. some antegrade flow across the RVOT and PV (see Chapter 29 for a more detailed discussion of this procedure [44]).

**Surgical repair**
Lillehei performed the first successful complete repair of TOF in 1954. The goals of repair then, as now, are:
- Maximal relief of RVOTO
- VSD closure
- Preservation of RV function in the short and long term.

The surgical technique has been well described [45]. After cardioplegic arrest, the repair is done using a transatrial-transpulmonary approach. The PV is examined through a longitudinal incision in the MPA, and, if necessary, a valve commissurotomy is performed. The RVOT is exposed through the RA and TV, and resection of the infundibular septum is carried out. The RVOT and MPA sizes are assessed using Hegar dilators, and if judged inadequate, the MPA incision is extended down towards the annulus and the RV free wall. A transannular patch can then be used to augment the size of the RVOT. Right ventriculotomy is avoided, if possible, to preserve RV function but may be necessary when there is moderate to severe infundibular obstruction requiring a transannular patch repair. A monocusp valve, fashioned from autologous pericardium or PTFE patch, can be placed in the RVOT to limit PI. The VSD is closed using a patch, and the ASD, if present, is also closed. Some surgeons prefer to leave a small atrial communication as a “pop-off” valve in case of RV dysfunction postoperatively. This will maintain LV preload at the expense of some cyanosis. In patients who have a coronary artery crossing the RVOT, a transatrial-transpulmonary repair is still feasible if the transannular incision is limited. Many of these patients, however, will require a valved RV–MPA conduit to avoid damage to the coronary artery.

The immediate adequacy of repair is assessed using several techniques. Immediate preoperative and intraoperative TEE is very useful in demonstrating gradients across the RVOT, showing residual VSDs, and assessing valves and ventricular function. The RV:LV pressure ratio can be measured, with less than 0.5–0.75 being considered acceptable. However, these pressure measurements in the early post-CPB period do not reflect measurements made at follow-up, and might lead to unnecessary revisions of the repair. Blood gas measurements from the vena cava and the MPA can also be used to detect residual shunts.

**Long-term surgical complications**
Despite excellent survival, many patients have residual sequelae from surgical repair: residual intracardiac shunts, TR, BPA stenoses, and aneurysmal dilatation of the RVOT might need surgical intervention. Cardiac MRI is becoming increasingly utilized in making volumetric and functional assessments of the RV and predicting clinical outcomes [46]. Chronic PI leads to progressive volume overload of the RV, producing ventricular dysfunction, reduced exercise tolerance, and increased incidence of arrhythmias. Many of these patients present for PV replacement, and the indications and timing of this procedure are well described [47]. Percutaneous PV replacement is available for some patients who do not have aneurysmal dilation.
of the RVOT [48]. Adverse outcomes such as reoperation for recurrent PI, heart failure, ventricular arrhythmias, and death are higher for adult patients with repair of TOF undergoing PVR who had a QRS duration of >180 milliseconds [49]. Also of note, pulmonary abscesses can be a concern in some adults, possibly due to decreased perfusion of the pulmonary parenchyma [50].

Anesthetic considerations

Unrepaired patients who do not have a palliative shunt can develop a “tet spell” at any time during the pre-CPB period. Worsening cyanosis and hypoxemia leading to cardiovascular collapse can occur without prompt and aggressive treatment. Particularly vulnerable periods are during anesthetic induction and before surgical stimulation, when reduced sympathetic tone causes a fall in the SVR leading to increased right-to-left shunting. Manipulation of the heart and great vessels by the surgeon might also result in sudden right-to-left shunting. The primary goals of managing a spell are to correct the hypoxemia by relieving the infundibular spasm and reversing the shunt. Some or all of the following maneuvers (Box 23.2) can be employed:

- **Increase the inspired oxygen concentration** to reduce hypoxic pulmonary vasoconstriction.
- **Administer phenylephrine, 5–10 μg/kg IV and titrate to increase SVR.**
- **Administer IV fluids** to increase right heart filling, potentially dilating the RVOT, and ultimately increasing CO and systemic blood pressure.
- **Apply abdominal compression**, such as by positioning the child in a knee-chest position, to increase RV preload and SVR.
- **Surgical compression of the aorta** to temporarily increase SVR. Care must be taken not to excessively limit flow distally, i.e. to the brachiocephalic vessels.
- **Administer a beta-blocker**, such as esmolol (50–200 μg/kg), and titrate to effect, utilizing its negative inotropic effect to relieve infundibular spasm. Propranolol (0.1 mg/kg given slowly) is also effective but is slower in onset.
- **Increase the depth of anesthesia with a volatile agent** to attenuate infundibular spasm via the anesthetic negative inotropic effect. Although halothane has historically been used for this purpose, an echocardiographic study showed that sevoflurane has less effect on the SVR index than halothane or isoflurane at 1.5 MAC [51]. Isoflurane is a poor choice because it is a potent vasodilator and also causes tachycardia, increasing contractility. Although morphine is frequently recommended for the treatment of “tet spells” in conscious patients, it produces too much vasodilation under anesthesia and is therefore not recommended.

If all these measures fail and the patient continues to deteriorate, the chest might have to be opened quickly, and the aorta manually compressed to reverse the shunting. In re-do sternotomies, extracorporeal membrane oxygenation (ECMO) can be a rescue therapy. If the sternum is already open, rapid institution of CPB is sometimes necessary.

<table>
<thead>
<tr>
<th>Box 23.2: Acute treatment of a “tet spell” or acute cyanosis/hypoxemia for patients with tetralogy of Fallot</th>
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<tbody>
<tr>
<td>• Reduce hypoxic pulmonary vasoconstriction</td>
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<tr>
<td>- Increase inspired oxygen concentration</td>
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<tr>
<td>• Increase left ventricular afterload</td>
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<tr>
<td>- Administer intravenous phenylephrine (5–10 μg/kg), and then titrate subsequent doses.</td>
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<tr>
<td>- Apply abdominal compression</td>
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<tr>
<td>• Surgical compression of aorta</td>
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<tr>
<td>• Increase right ventricular preload</td>
</tr>
<tr>
<td>- Administer intravenous fluid boluses</td>
</tr>
<tr>
<td>- Apply abdominal compression</td>
</tr>
<tr>
<td>• Treat right ventricular infundibular spasm</td>
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<tr>
<td>- Administer intravenous esmolol (50 μg/kg) and then titrate subsequent doses</td>
</tr>
<tr>
<td>- Increase the depth of anesthesia with sevoflurane</td>
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<tr>
<td>• Emergency extracorporeal support if other measures fail</td>
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<tr>
<td>- ECMO or CPB via femoral or trans-sternal routes</td>
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Perioperative anesthetic management for surgical palliation

Many patients who require surgical palliation are critically ill due to severely reduced PBF. They might be mechanically ventilated and on a PGE₁ infusion to maintain ductal patency. If IV access is available, anesthesia can be induced with a combination of ketamine and fentanyl and maintained with low concentrations of a volatile agent. It is important to maintain adequate SVR to limit right-to-left shunting through the VSD; in this regard, sevoflurane is a good choice, as this has the least effect on SVR [51]. The myocardial depressant effect of volatile agents is also useful in limiting infundibular spasm. Low SVR is treated with fluid boluses and phenylephrine. Inotropes are best avoided, as these will worsen infundibular spasm by increasing heart rate and contractility. If there is no IV access, induction can be carried out rapidly and smoothly with sevoflurane. An alternative is to use intramuscular ketamine and rocuronium in unstable patients who might not tolerate the vasodilation from volatile agents. Central venous access is obtained for the infusion of fluids and vasoactive agents. A radial arterial line is placed on the side opposite to that of the planned mBTS in order to get a true assessment of the blood pressure, because after the shunt is opened there might be significant “steal” from the ipsilateral subclavian artery. A femoral arterial line can also be placed, as long as care is taken to observe for evidence of distal lower extremity ischemia.

Most mBTSs are performed via a thoracotomy. The median sternotomy approach is used for central shunt placement if the surgeon feels that the patient will not tolerate lung retraction or side-clamping of the PA, and there is a possibility that CPB might be required. Low-dose heparin (100 units/kg) is administered prior
to shunt placement. Lung retraction can severely impair oxygenation and ventilation, and intermittent reinflation might be required. Similar hypoxemia can occur during partial clamping or obstruction of the MPA during the construction of the anastomosis. This is usually managed with fluids, vasopressors, and ventilation adjustments to reduce PVR. For central shunts, partial clamping of the ascending aorta is required, sometimes poorly tolerated in the presence of LV dysfunction, and carefully titrated inotropic support with low-dose epinephrine or dopamine can help to maintain cardiac contractility without inciting obstructive RV infundibular spasm. Once the shunt is open, oxygen saturation often improves immediately. However, blood pressure can drop significantly due to diastolic run-off, requiring volume infusion and vasopressor support. This is especially true because the PDA is still open and cannot be easily ligated if the usual right thoracotomy approach is utilized. If the diastolic pressure becomes very low, coronary flow can be reduced. Vasopressors, i.e. phenylephrine, vasopressin, and norepinephrine, may be required until the PDA closes to provide enough coronary perfusion pressure. Ventilation and inspired oxygen are adjusted to mimic spontaneous, non-anesthetized blood oxygen and carbon dioxide levels for an accurate assessment of the shunt flow. An oxygen saturation of near 80–85% is optimal as this estimates balanced pulmonary and systemic blood flow. A high saturation suggests pulmonary over-circulation and the shunt size might have to be reduced. Conversely, a low saturation suggests inadequate PBF, and a larger diameter shunt might be needed. In cases of persistent hypoxemia after apparently uneventful shunt placement via a thoracotomy, it is important to rule out the possibility of endobronchial intubation, because failure to do so might lead to unnecessary shunt revision or even sternotomy.

Postoperative care for surgical palliation

After chest closure, the patient is transferred to the cardiac ICU and kept on a ventilator for 12–24 hours. Increased PBF can cause the patient to become acutely unstable due to pulmonary edema or pulmonary hemorrhage (which can be unilateral). Diastolic hypotension can cause myocardial ischemia, requiring close monitoring and treatment. Other complications include injury to the phrenic and recurrent laryngeal nerves, Horner’s syndrome, chylothorax, and shunt thrombosis. Briefly disconnecting the patient from the ventilator and auscultating the end of the endotracheal tube can clinically confirm patency of the shunt. The murmur is transmitted via the tracheal tube due to the proximity of the shunt to the bronchus. When it is determined that there is no excessive post-surgical bleeding, a low-dose heparin infusion is started (6–10 units/kg/hour) to maintain shunt patency. After enteral intake has begun, patients are prescribed low-dose aspirin until the time of complete repair. Platelet transfusions are generally avoided for patients undergoing shunt placement due to the risk of shunt thrombosis.

Perioperative anesthetic management for surgical repair

There are additional considerations for complete repair using CPB. The anesthetic induction strategy is similar to that for shunt placement. Generally, we utilize a total fentanyl dose of 15–50 μg/kg and administer inhalational agents to supplement anesthesia. The lower dose of fentanyl usually allows for extubation within 4–8 hours after surgery. A ketamine infusion has been shown to provide more hemodynamic stability by preserving SVR in the pre-CPB period when compared with isoflurane [52]. A TEE probe is placed if patient size permits. If TEE is not possible or unavailable, epicardial echocardiography can be performed post-CPB to assess repair. In addition to routine monitors, brain oxygen saturation trends can be followed with near-infrared spectroscopy.

During the rewarming phase of CPB, preparations are made for weaning from CPB. The following problems should be anticipated:

- **RV dysfunction** can result, especially if the transannular incision was extended down along the RV free wall. The mainstays of treatment are fluid loading to higher filling pressures, inotropic support, and reduction of RV afterload. Dopamine (5 μg/kg/min) and low-dose epinephrine (0.04 μg/kg/min) are useful inotropic agents. Milrinone (0.375–0.75 μg/kg/min) can also be used to help RV function and reduce PVR. Due to RV hypertrophy and diastolic dysfunction, high filling pressures might be needed to maintain CO. An RA and/or a LA pressure line can be useful in optimizing preload. Ventilation is adjusted to optimize oxygenation/ventilation while minimizing airway pressures prior to weaning.

- **Arrhythmias and heart block are common** after VSD repairs because of the close proximity of the conduction system. Epicardial pacing might be needed to accomplish weaning from CPB. In most instances, heart block is a transient phenomenon due to the edema around the VSD patch. If it does not resolve after 7–10 days, permanent pacing might be required. Junctional ectopic tachycardia occurs in approximately 10% of patients after surgery, and is an important cause of morbidity, mortality, and increased ICU stay. The usual onset is 12–24 hours after surgery, and is characterized by heart rates above 170/min and AV dissociation. The loss of AV synchrony can produce serious hemodynamic deterioration. Possible risk factors include long bypass times, high inotropic requirements, and surgical intervention near the AV node. Treatment consists of sedation, normalization of electrolytes (especially magnesium), cooling to 34–35°C, and IV amiodarone [53]. Amiodarone can be used prophylactically to reduce the incidence of junctional ectopic tachycardia [54].
Post-CPB bleeding is usually due to the extreme hemodilution and the effects of CPB on platelet function, and often requires transfusion of multiple component blood products. The use of antifibrinolytics such as epsilon-aminocaproic acid or protease inhibitors such as aprotinin (withdrawn from the market by the manufacturer at the time of writing) can reduce post-CPB bleeding and minimize the use of blood products.

Presence of a residual VSD can be problematic. Due to the low-resistance RVOT, this will place an excessive volume load on the LV and will be poorly tolerated. A defect larger than 3 mm requires further hemodynamic evaluation by quantifying the shunt and measurement of left atrial pressure, to decide whether to return to CPB. Two-thirds of the defects less than 3 mm detected by intraoperative TEE are not detectable by the time of hospital discharge [55].

Hyperdynamic RVOT limiting stroke volume, particularly with tachycardia. Some centers still employ propranolol preoperatively to limit infundibular spasm; β-blocker withdrawal sometimes necessitates esmolol infusion in the early postoperative period. This scenario is less common in the modern era of early repair.

Other important complications include residual RVOTO that might require revision and TR. Due to PI and high RV cavity pressure, the patient poorly tolerates TR.

Postoperative care for surgical repair

Once the chest is closed, the patient is transferred to the ICU. Analgesia is provided with a continuous morphine infusion (20–40 µg/kg/hr), and supplemented with midazolam or dexmedetomidine sedation. Hemodynamically stable patients with minimal bleeding are good candidates for early extubation either in the operating room or later in the ICU, but usually within 4 hours. After the patient is extubated, analgesia can be reliably provided with a combination of acetaminophen and a non-steroidal anti-inflammatory agent such as ibuprofen.

Patients with RV diastolic dysfunction require high filling pressures in order to maintain adequate CO.

Following complete repair, RV dysfunction, heart block, arrhythmias, and bleeding should be anticipated.

Pulmonary stenosis with intact ventricular septum

Incidence, anatomy, and natural history

Pulmonary stenosis with intact ventricular septum (PS/IVS) is a relatively common malformation, accounting for 8–10% of congenital heart defects and with an incidence of 1 in 2,000 births worldwide. There may be a slightly higher birth prevalence in Asia when compared with European and North American populations [56]. PS can be further divided into three groups: valvular, subvalvular, or supravalvular. Valvular is the most common by a significant margin, as 80–90% of reported PS is valvular, with the remaining 10–20% being subvalvular or supravalvar (including stenosis of the BPs) [57].

In valvular PS, the PV is dome-shaped with a narrow, centrally placed orifice. The RV is usually normal in dimension with the exception of the infundibular hypertrophy that occurs as a result of outflow obstruction. Undeveloped raphes (false commissures) can be seen. Valvular PS is frequently associated with Noonan syndrome, but can also be associated several other congenital heart defects such as ASD, EA, double outlet right ventricle, and transposition of the great arteries [57].

Subvalvular PS can be divided into two types: infundibular or subinfundibular. Infundibular PS is usually as part of TOF, as isolated infundibular PS is quite rare [56]. It is notable that infundibular PS can also be due to reactive hypertrophy of the infundibulum in valvular PS. Subinfundibular PS can occur within the RV cavity due to abnormal hypertrophied muscle bands that run between the ventricular septum and the anterior wall, effectively dividing the RV cavity into a proximal high-pressure chamber and a distal low-pressure chamber, known as a double-chambered RV (DCRV). While hypertrophied muscle bands typically cause DCRV, the high-velocity jet passing through a small VSD may also result in DCRV [57].

Supravalvular PS can be seen with congenital rubella and several syndromes such as Williams, Noonan, Alagille, DiGeorge and Leopard syndromes [57]. The stenosis can be localized to MPA, at the bifurcation, and at the BPs. If the stenosis is in the MPA, there is often post-stenotic dilation of the MPA and sometimes of the LPA as well. The etiology of the defect is unknown, but there is likely a genetic factor as the incidence in the defect in siblings of the affected patient is 2–4%.

The natural history of PS begins in utero at approximately 20 weeks’ gestation. At this point, fetal echocardiography

KEY POINTS: TETRALOGY OF FALLOT

- Hypercyanotic spells are treated with oxygen, phenylephrine, IV fluid, esmolol, deepened sevoflurane anesthetic, and abdominal compression.
- During BT shunt placement, difficulties might be encountered with oxygenation and ventilation, and later hypotension after the shunt is open.
- Postoperative ventilation is recommended for 12–24 hours after BT shunt placement because of the risk of pulmonary edema.
- Coronary arteries that cross the RVOT inferiorly restrict the ability to utilize a transannular patch repair.

- Postoperative care for surgical repair

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- Patients with RV diastolic dysfunction require high filling pressures in order to maintain adequate CO.

- Following complete repair, RV dysfunction, heart block, arrhythmias, and bleeding should be anticipated.

- Pulmonary stenosis with intact ventricular septum

Incidence, anatomy, and natural history

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Supravalvular PS can be seen with congenital rubella and several syndromes such as Williams, Noonan, Alagille, DiGeorge and Leopard syndromes [57]. The stenosis can be localized to MPA, at the bifurcation, and at the BPs. If the stenosis is in the MPA, there is often post-stenotic dilation of the MPA and sometimes of the LPA as well. The etiology of the defect is unknown, but there is likely a genetic factor as the incidence in the defect in siblings of the affected patient is 2–4%.

The natural history of PS begins in utero at approximately 20 weeks’ gestation. At this point, fetal echocardiography
can be done and thus delineation of cardiac anatomy is possible. As the child ages, stroke volume (SV) increases as well, from about 5 mL in the infant to 70 mL in a full-grown adult. To match the increased stroke volume, the valve orifice needs to enlarge or the RV systolic pressure (RVSP) needs to increase. Generally if the area of the valve opening enlarges proportionally to the increasing SV, RVSP will not increase. However with severe stenosis, the RVSP increases and can lead to dilation and eventual congestive failure of the right heart. Many patients with PS are asymptomatic at birth, but as they age they may suffer from dyspnea, fatigue with exertion, supraventricular arrhythmias, and infective endocarditis. While some children may develop heart failure early on, many survive into the fourth decade of life [58].

Pathophysiology
In its most severe manifestation, PS/IVS presents in the neonatal period with cyanosis and right heart failure. However, most children develop signs and symptoms more gradually, depending on the severity of the PS and the relative sizes of a PFO or ASD. Many patients are initially identified by the presence of a harsh systolic ejection murmur and perhaps a thrill over the PV auscultation area. There is often post-stenotic dilation of the BPs that can be visible on chest roentgenogram. Radiographic cardiomegaly is a late sign, coincident with signs of failure. The ECG often shows right axis deviation, prominent P waves, and evidence of RV hypertrophy. Echocardiography with Doppler evaluation can be used to grade the severity of the valve as well as peak and mean gradients; serial measurement is used for follow-up studies. MRI can be used to study anatomy and establish the exact location of the stenosis (supravalvular, valvular, or subvalvular) as well as prevent the need for exposure to ionizing radiation, as with multi-slice CT scans. Cardiac catheterization allows one to directly measure pressure gradients and evaluate anatomy via angiography and provide therapeutic options to the patient via balloon valvuloplasty.

Surgical and transcatheter approaches and outcomes
Symptomatic patients and those with severe gradients (Doppler-derived peak gradient of > 64 mmHg or mean gradient > 40 mmHg) and impending RV failure are treated primarily with balloon valvuloplasty, which has replaced surgery as the first-line treatment [59]. However, in cases involving a hypoplastic annulus, severely dysplastic valve, and other associated congenital cardiac lesions, surgery may be the preferred initial option [57]. Percutaneous balloon valvuloplasty can be used repeatedly for recurrent PV stenosis. The incidence of PI after balloon valvuloplasty is 80% but is usually mild in clinical severity. Balloon valvuloplasty is typically considered successful once the valvular gradient is < 30 mmHg [57]. Complications, although rare, include transient bradycardia and hypotension with balloon inflation, transient/permanent AV block, tricuspid papillary muscle rupture and pulmonary artery rupture. Occasionally a β-blocker such as esmolol is needed to reduce contractility in a hyperdynamic RV after valvuloplasty.

Surgical repair can be attempted with or without CPB via a median sternotomy approach. With the CPB-assisted technique, a transverse incision is made in the MPA. Fused valve leaflets are incised. The annulus can be enlarged with Hegar dilators. Subvalvular obstruction in the infundibular region can be excised.Rarely,a transannular patch might be needed. A right atriotomy is used to close a PFO or ASD and an infundibular resection through the TV, if needed. Surgical pulmonary valvotomy can also be performed off-CPB via a transventricular approach through a purse-string suture in the anterior RV. Hegar dilators are inserted in increasing diameters across the valve. The CPB pump can be kept primed and on standby for this approach. With either surgical technique, residual valve gradients can be measured utilizing needle pressure transducers. In isolated PS, the perioperative mortality for surgical repair approaches zero. Occasionally it is impossible to repair the valve surgically, and valve replacement is indicated. Non-mechanical valves are preferred to mechanical valves, as the risk of thrombosis in pulmonary mechanical valves is higher than mechanical valves in the aortic position [57]. Pulmonary homograft is an option that many surgeons consider, depending on institutional availability.

Anesthetic considerations
Ensuring effective inotropic therapy, adequate diuresis, and correcting metabolic acidosis and electrolyte abnormalities medically optimize the patient with CHF prior to surgery. Neonates with critical PS should be stabilized with PGE1 and taken for cardiac catheterization without delay. Most patients will be eligible for elective repair. Inhalation induction vs. IV induction with opioid and muscle relaxant is appropriate, with the latter a better choice for children with moderate to severe reduced RV function. After CPB, the RV filling pressures must be adequate while avoiding high pulmonary pressure to enhance forward right-sided CO. Pulmonary vasodilators begun in the early postoperative course or in the late CPB period might increase pulmonary flow and reduce RV afterload. Although most patients tolerate PI that results from either open or closed pulmonary valvotomy, inotropic support is often needed to assist the transient RV dysfunction that is frequently present after anterior right ventriculotomy with the closed approach. Inotropic support is used judiciously in patients who might have a dynamic subvalvular obstructive component due to infundibular hypertrophy, but might be needed to achieve adequate RV function for a few days after repair. Residual infundibular hypertrophy often resolves with time after the valvular obstruction is relieved. Effective postoperative analgesia and sedation can be provided with opioid and dexmedetomidine infusions as well as IV acetaminophen.
KEY POINTS: PULMONARY STENOSIS WITH IVS

- Valvular PS is most common at 80–90%, with sub-valvular and supravalvular types making up the remaining 10–20%.
- Successful percutaneous balloon valvuloplasty results in a transvalvular gradient of < 30 mmHg.
- Esmolol may be useful in reducing contractility in a hyperdynamic RV after percutaneous balloon valvuloplasty.
- In the immediate period after repair, RV filling pressures must be adequate while avoiding high pulmonary artery pressures if possible.

Pulmonary atresia with intact ventricular septum

Incidence, anatomy, and natural history

Unlike PS/IVS, PA/IVS does not have a familial association. The defect comprises approximately 1.0–1.5% of congenital heart defects. Although the etiology of the defect is unknown, the inciting event appears to be severe intrauterine RVOTO, leading to maldevelopment of the TV, RV, and coronary arteries. The degree of abnormality varies with the gestational age at which the RVOTO occurs.

Patients with a diminutive RV, small TV, and extensive RV to coronary artery communications would be presumed to have incurred PA at an earlier stage of gestational development. Multiple morphologic abnormalities occur with this lesion, all of them proximal to the PV (in contrast to PA with VSD in which the major associated defects occur distal to the valve). The PV is usually tricommissural, with fused leaflets approximately 75% of normal diameter; however, multiple configurations, including unicuspoid or quadricuspid configurations, can occur [60]. There is almost always a PFO or secundum ASD, which is restrictive in 5–10%. The TV is usually smaller than normal, but can range from extremely stenotic to the dilated annulus of EA (5–10%). The RA is dilated proportionately to the degree of TR. The RV is hypertrophic with reduced size of the cavity.

In about 50% of cases, there are endothelial-lined blind channels within the RV myocardium known as sinusoids that are most likely remnants of vessels providing nutrients to the ventricles prior to the formation of coronary arteries. They appear to persist secondary to RV hypertension [60]. These sinusoids are in direct communication with the RV cavity and can form RV to coronary artery fistulae. The prevalence of these sinusoids is inversely proportional to the diameter of the TV, RV cavity size, and magnitude of TR, but directly proportional to RV systolic pressure, presumably because in the presence of TI, RV hypertension is limited. In the least affected individuals, RV blood is sent as part of a dual blood supply to small areas of myocardium in tandem with normal aortocoronary flow. But approximately 20% of patients with PA/IVS have an absence of anterograde aortocoronary flow, a finding confirmed with either cardiac catheterization (Figure 23.10) or 64-slice computed tomography (CT) [61]. In these patients, the coronary bed is perfused with poorly saturated systemic venous blood directly from the RV, resulting in a chronically ischemic myocardium. In the most severely affected patients, aortocoronary connections will be absent and only an RV-dependent coronary circulation will supply the RV myocardium [62]. Sometimes the PV is seemingly intact, but with fused commissures. Most often, there is a fibrous tissue at the ventriculoarterial junction. The pulmonary arteries usually have normal branching and can be hypoplastic in about 6% of cases. There is almost always a PDA. The LA is enlarged and hypertrophic, sometimes exhibiting fibroelastosis. Subaortic stenosis can result from bulging of the ventricular septum into the LV due to RV hypertension.

Without treatment, PA/IVS results in death in 50% of neonates, and in 85% of infants by 6 months of age. Fetuses with small, hypertrophied ventricles often survive to birth; whereas those with dilated RVs and severe TR may die in utero with fetal hydrops. Postnatal death is usually due to hypoxemia and, with the closure of the ductus arteriosus, eventual myocardial ischemia and infarction.

Pathophysiology

For those neonates who do not develop hydrops and survive through birth, moderate to severe TR will have allowed the RV pressure to remain low enough that sinusoids and coronary fistulae will not have developed. Alternatively, if TR is mild or nil, the neonatal RV will be small and hypertrophic with marked systolic hypertension, and coronary fistulae might be present. The increased flow across the foramen ovale in utero causes a volume overload of the left heart, resulting in neonatal LV hypertrophy and dilation, and possible aortic root dilation. The affected newborn is dependent upon the PDA and is resuscitated with PGE₁. Generally, the left heart functions normally and CO is maintained with the presence of an adequate PDA. If there is LV hypertrophy from septal hypertrophy/LV outflow tract obstruction, the presence of coronary fistulae can result in myocardial ischemia. Effectively, the newborn with PA/IVS manifests a single-ventricle physiology. TR is common, partly because of the RVOTO, and, in approximately one-third of cases, due to structural abnormalities of the TV. Over 90% of patients will present with cyanosis and a ductal flow murmur within the first 3 postnatal days.

The ECG reveals small RV forces and often a large P wave, indicative of RA enlargement. Chest roentgenogram often shows decreased to normal pulmonary vascular markings, depending on the amount of ductal flow. The cardiac silhouette is normal unless RA and RV enlargement occur due to severe TR. Echocardiography can
Figure 23.10  Pulmonary atresia with intact ventricular septum in a 1-day-old infant. A National Institutes of Health (NIH) catheter has been placed prograde into the right ventricle (RV) via a hypoplastic tricuspid valve for a contrast hand injection. There is mild tricuspid regurgitation. Numerous coronary sinusoids from the RV cavity to both right coronary artery (RCA) and left coronary artery are demonstrated. Contrast faintly opacifies the aorta (Ao) retrograde through a dilated left main coronary artery (LMCA). (A) Frontal view. (B) Lateral view. RV outflow tract ends at the atretic pulmonary valve (APV). (Source: Eudice E. Fontenot, MD. Reproduced with permission.)

define the RVOT, RV dimensions, the TV, and the PDA. RV pressure can be derived from Doppler measurement of the TR. Ventricular function can be assessed, but dependency of coronary blood flow cannot be determined solely with echocardiography. Cardiac catheterization is essential in all cases to define major stenoses and fistulae in the coronary anatomy, but rarely serves to avoid subsequent surgical repair [63].

Surgical and transcatheter approaches and outcomes

In the early 1960s, palliative shunts and closed pulmonary valvotomies were done. However, survival was dismal given that an estimated 2.5% of patients survived to 3 years of age. Right ventricle outflow procedures were combined with systemic-to-pulmonary arterial shunts in the 1970s. Since that time, repair techniques have varied among surgeons, partly based on the spectrum of anatomic dysmorphology and partly on the individual surgical outcome experiences. Current corrective procedures include:

- Neonatal RVOT patch augmentation with continued infusion of PGE\(_1\) (average of 6 days)
- Neonatal RVOT patch augmentation with concurrent systemic artery-to-PA shunt
- Pulmonary valvotomy (open or closed) and a systemic-to-pulmonary arterial shunt

Success rates in achieving ultimate biventricular repair have varied from 40% to 60%. However, all congenital heart surgeons avoid RV decompression if there is a complete dependency of myocardial blood supply on the RV. In such cases, initial palliation usually consists only of placing a systemic-to-pulmonary arterial shunt. Some surgeons have maintained RV-dependent coronary perfusion during CPB by pressurizing the RV with a second arterial cannula via the RA with bicaval venous cannulation [65]. Different surgeons manage patients with partial RV dependency for myocardial blood supply variably, but regional LV wall motion abnormalities can worsen after RV decompression.

The major determinants of the most appropriate surgical approach for a particular patient are:

- Degree of RV and TV hypoplasia
- Presence of RV-dependent coronary circulation
- Degree of TR.

The surgical options include (Figure 23.11):

- Complete biventricular repair with later closure of the interatrial communication
- Biventricular repair with allowable mixing of blood at the atrial level (ASD/PFO left open, or surgically adjustable ASD), but using the RV to pump blood to the lungs
- One-and-a-half-ventricle repair using a BCPC to reduce RV load
- Modified Fontan procedure
- Cardiac transplantation as a last resort.

Reddy and Hanley [66] outline the goals of initial surgical therapy as follows:

- Minimize mortality.
- Promote growth of the RV such that chances are improved for a later two-ventricle repair.
- Minimize the need for non-definitive later surgeries.
They point out that:
• Survival after systemic artery-to-pulmonary shunt is at least as successful as any other initial surgical procedure.
• The RV will not grow if it is not decompressed and RVOT relief will be needed if two-ventricle repair is thought to be possible later.
• The ultimate functional potential of the RV is often unclear in the neonate with PA/IVS. The initial procedure often determines the final repair/palliation outcome.

Catheter-based PV perforation (PVP) and balloon valvuloplasty has been used as a treatment modality in PA/IVS with a non-RV-dependent coronary circulation (non-RVDCC) for several years with promising results [67]. In this procedure the PV is perforated with a wire, laser, or radiofrequency energy and then the PV is dilated with one or more balloons [68]. The PDA may need to be stented during or subsequent to this procedure if PBF is deemed inadequate.

**Anesthetic considerations**

Despite the variety of surgical options available for PS/IVS and PA/IVS, there are some general considerations. For any patient with a small hypertrophic, hypertensive RV, RV filling pressures must be maintained such that the RV cavity does not collapse, causing it to be an ineffective pump. This is especially important after RV outflow obstruction is relieved with the biventricular repair. Inotropic RV support is often essential, as RV dysfunction is present after CPB in the presence of increased afterload of an unadjusted pulmonary vascular circulation. Minimizing ventilation pressures and vasodilating the pulmonary vasculature with drugs such as milrinone (0.375–0.75 μg/kg/min) or dobutamine (5–10 μg/kg/min) helps to reduce RV afterload. With severe pulmonary hypertension, nitric oxide is useful in the immediate post-repair period to aid in pulmonary vasodilation until the vascular bed adjusts to the increased flow. Also with biventricular repair, an acute increase in PBF can cause pulmonary edema, resulting in bronchospasm and impairment of oxygenation. The one-and-a-half-ventricle repair requires a balance of adequate preload to a partially unloaded RV and maintenance of low PVR for upper body passive venous return to the pulmonary vasculature. Along with the ventilation and pharmacological maneuvers, positioning patients with the head up 30° will aid in augmenting upper body venous return to the pulmonary vascular bed. When RV function becomes adequate to support the work of breathing, spontaneous respiration in an extubated patient will generate a relative negative intrathoracic pressure that aids in boosting PBF.

With palliative aortopulmonary shunt placement, consideration is given to continued balance of pulmonary and systemic parallel circulations. Low CO in the postoperative period might result from unrecognized RV-dependent coronary circulation or from a “circular shunt.” The latter occurs in patients who have had a transannular patch.
and a systemic-to-pulmonary arterial shunt. Because the transannular patch produces free PI, blood ejected from the LV flows through the systemic-to-pulmonary arterial shunt and enters the RV in a retrograde fashion. If there is significant TR, blood flows back into the RA and then into the LA through the interatrial communication (Figure 23.6). This flow effectively “steals” blood from the systemic circuit and can lead to hypoperfusion of the distal organs and metabolic acidosis. Conservative measures such as raising the PVR and reducing the SVR might be helpful, but often surgery is needed to revise the shunt and treat TR.

Sedation with benzodiazepines and \( \alpha_2 \) agonists and pain control with opioid infusions such as morphine are balanced with the patient’s condition, the anticipated duration of mechanical ventilation, and the time needed for pulmonary vascular adjustment/RV recovery. Infusing low-dose heparin at 6–10 units/kg/hour might reduce the incidence of early shunt thrombosis. Later, after enteral feeding has resumed, low-dose aspirin is used prophylactically to help maintain shunt patency.

### Key Points: Pulmonary Atresia with IVS
- Unlike PS/IVS, PA/IVS does not have a known genetic association, but seems to result from severe intrauterine RVOTO.
- Sinusoids are present in about 50% of cases.
- Approximately 20% of patients with PA/IVS do not have anterograde aortocoronary flow and have a chronically ischemic myocardium with RVDCC.
- Mortality in untreated infants is 50% by 1 month and 85% by 6 months of age.
- For any patient with a small, hypertrophic, hypertensive RV, filling pressures must be maintained to prevent RV collapse.
- Filling and RV pressure must be maintained for patients with RVDCC at all times to prevent “coronary steal” from the myocardium, even while on CPB.

### Pulmonary atresia/VSD/MAPCAs

#### Incidence, anatomy, and natural history

Pulmonary atresia/VSD/MAPCAs is a complex and rare defect in which much morphological variability surrounds the source of PBF. This leads to diverse clinical presentations and multiple options for surgical correction. The Baltimore Washington Infant study reported an incidence of 0.07 per 1,000 live births for PA/VSD/MAPCAs, which represented approximately 1.5% of all congenital heart defects [69].

In its simplest form, with normal pulmonary vasculature, this lesion can be considered an extreme variation of TOF. However in most cases, there is great morphologic variability regarding pulmonary artery architecture and sources of PBF, posing major challenges for corrective surgery. With PA, there is no continuity between the RV and the pulmonary trunk. The VSD is usually large and malaligned. The PAs can be normal in size or have varying degrees of hypoplasia to even complete absence. The BPAs can be confluent or non-confluent. An additional major source of PBF is derived from MAPCAs arising from the aorta or its major branches. MAPCAs are likely dilated bronchial arteries, and do not have the same growth potential as pulmonary arteries. In addition, MAPCAs appear to eventually develop stenosis at the point of their origin, and the area supplied by the MAPCA will eventually become underperfused. A given lung segment can be supplied solely from the true PAs, solely from the MAPCAs, or from both. A classification system has been proposed, based on the morphology of the PAs and MAPCAs, which can be useful in surgical decision-making [70] (Figure 23.12).

Chromosomal abnormalities such as partial 22q11 deletion or aneuploidy are commonly associated with PA/VSD/MAPCAs. In terms of the postnatal course, three distinct groups have been described with differing outcomes. In the first group, the ductus arteriosus is the single aortopulmonary connection. Without intervention, more than 50% die by 6 months of age and 90% by 1 year. The second group has some MAPCAs present; in this group 50% die by 3–5 years of age and 90% within 10 years if untreated. Finally the third group has multiple and large MAPCAs. In the third group, only mild cyanosis is noted on physical exam, with no evidence of CHF. Untreated patients in this group typically reach adulthood and into the third decade, but eventually succumb to pulmonary vascular disease resulting in Eisenmenger syndrome [71].

#### Pathophysiology

The great variability in the sources of PBF determines the natural history and management options of this lesion. Excessive PBF through the collateral arteries will produce pulmonary congestion and a clinical picture of CHF. Moderate stenoses of the collateral arteries can result in a balanced PBF with arterial saturation of around 80% and minimal symptoms. Severe stenoses of the collateral arteries or a ductal-dependent circulation will lead to inadequate PBF, cyanosis, and hypoxemia. Patients with a balanced blood flow can even survive to adulthood with minimal symptoms, but eventually LV failure will ensue from chronic left-to-right shunting and volume overload.

Although the diagnosis of PA/VSD/MAPCAs can be made with echocardiography, virtually all patients require cardiac catheterization to delineate the true pulmonary artery architecture and collateral artery anatomy in order to plan the optimal surgical approach. Magnetic resonance angiography with three-dimensional reconstruction of the images is also becoming increasingly useful in delineating the complex anatomy (Figure 23.13).
Surgical and transcatheter approaches and outcomes

Based on anatomical and physiological criteria as well as the age of the patient (Box 23.3), a clinical decision-making algorithm is a useful way to summarize the management of this complex condition [72] (Figure 23.14). The ultimate goal of surgery is to achieve a biventricular repair by:

- Creating a pulmonary vascular bed by introducing or utilizing existing sources of PBF. The new pulmonary vascular bed must be capable of receiving the entire RV output without imposing too high a ventricular afterload.
- Restoring continuity between the RV and the reconstructed pulmonary vascular bed.
- Closing the VSD.

Box 23.3: Factors contributing to the surgical plan for pulmonary atresia/ventricular septal defect/major aortopulmonary collateral arteries

- Size and morphology of the native pulmonary arteries
- Branching of the native pulmonary vasculature
- Quantity of pulmonary blood flow from all sources
- Age of the patient

It might not be possible to achieve all these goals in all patients. An inadequate pulmonary vascular bed will eventually cause RV failure due to chronic increased afterload. The post-repair RV systolic pressure should optimally be 50% or less than the LV systolic pressure for a successful outcome.
In patients with hypoplastic native PAs, the initial surgical priority is establishing increased blood flow through these arteries to promote their growth. This is achieved either by an RV–MPA conduit or an aortopulmonary shunt (variously employed as a central shunt, Melbourne shunt or aortopulmonary window). PBF from the RV to the BPAs can be gradually enhanced with subsequent operations by adding or enlarging an RV–MPA conduit and from the BPAs to the lung tissue by growth of the native pulmonary arterial bed and/or by connecting MAPCAs to the BPAs.

“Unifocalization” (creating a single source of PBF to each lung), a palliative surgical method of detaching as many MAPCAs from the aorta as possible and attaching them to the BPAs in order to create a pulmonary vascular bed with unobstructed flow originating from the RV, was begun in the late 1970s (Figure 23.15). This centralization of multiple sources of PBF can be done in a single-stage midline approach (including VSD closure, if feasible) or as a multi-stage procedure involving sequential bilateral thoracotomies, followed by a definitive intracardiac repair through a median sternotomy. However, some centers are obtaining good results with a single-stage unifocalization and repair, and this approach does have many advantages. It avoids subjecting the patient to multiple surgeries, which, if performed via thoracotomies, can make subsequent procedures extremely hazardous (especially lung transplants) due to increased adhesions and the potential for massive bleeding. Additionally, serious neurological injury can occur during CPB-assisted unifocalization, because increased run-off into the pulmonary circuit can result in cerebral hypoperfusion despite apparently adequate pump flows. Obviously, a single-stage approach will not be applicable in all patients, and this group will need a systemic-to-pulmonary artery shunt or an RV-to-pulmonary artery conduit to allow growth before definitive repair.

The limiting factor for the extent of unifocalization is often the resulting pulmonary artery pressure. Malhotra et al. [73], in a series of 462 patients, were able to complete single-stage unifocalization in 76% of patients, with intracardiac repair at the initial operation in 56%, and at 5 years 90% were completely repaired. In the 15-year span the series was completed, the operative mortality was 5.9%, and survival at 5 years was 85.5%. In this same report, they described intraoperative pulmonary artery pressure measurement after unifocalization as an additional consideration for a successful surgery. While the patient is still on CPB and post-unifocalization, the MPA is cannulated with a separate cannula and roller pump head, a pressure monitoring catheter is placed, lungs are inflated to normal tidal volume, and flow is started in the pulmonary arterial system and increased to approximately one indexed CO. A mean pulmonary artery pressure of less than 25 mmHg reliably predicts a systolic RV:LV pressure ratio at or below 50%.
Unifocalization is beneficial in that it is an existing source of vasculature that can be used to create a pulmonary vascular bed for a young infant or child. However, later follow-up of unifocalized MAPCA anatomy reveals that a majority become thrombosed, severely stenotic, or merely fail to grow [74]. As a consequence, some patients will gradually develop worsening pulmonary hypertension and reduced PBF, resulting in gradually worsening exercise intolerance and RV failure. Thus unifocalization is not universally advocated as a means of augmenting the pulmonary vascular bed.

Some surgical centers propose that pulmonary arterial growth can be accomplished with gradual shunting of blood to the diminutive MPA and BPA augmentation. Brizard et al. [75] maintain that:

- Hemodynamics of PBF in the long term is related to the compliance and size of the native pulmonary arteries.
- Unifocalized MAPCAs often do not grow, and, in fact, sometimes restrict growth of the BPA on which they have been attached.
- Reconstructed BPAs, such as those augmented with a pericardial roll, are poorly compliant.
- Large MAPCAs (that are not unifocalized) rarely cause pulmonary hypertensive vascular disease, a condition that develops very slowly.
- Almost all patients with PA/VSD/MAPCAs have an MPA, even if it is tiny. The exceptions are those with bilateral PDAs, but those patients often have beneficial arborization.
- Tiny pulmonary arteries will grow if a source of blood flow is provided.

They recommend a contrast CT scan near 1 week of age to reveal the pulmonary vasculature, and then a central shunt in the first 4–6 weeks of age. Pulmonary overcirculation does not occur due to the restrictions of the small pulmonary arterial branches. Increased flow from the central shunt then enhances growth not only of the BPAs and distal pulmonary arterial tree, but of the MPA. Then at 3–4 months of age, the pulmonary arteries are evaluated again for hypoplasia or stenosis with contrast CT, magnetic resonance angiography, or catheterization. A second operation is then performed shortly afterward at 4–6 months of age to take down the central shunt, place an RV–MPA conduit, and repair areas of pulmonary arterial stenosis or hypoplasia. A third operation after repeat imaging studies is eventually done as a complete repair (including VSD closure) or limited to replacement of the RV–MPA conduit with a valved conduit with or without BPA enhancement with autologous pericardium or expanded PTFE patches. Early results by the same institution [76] for 25 consecutive patients with PA/VSD/MAPCAs showed that 20 could be managed with this surgical regimen. Twelve out of the 20 underwent a complete repair between the ages of 11 and 48 months. These 12 had a post-repair median RV:LV pressure ratio of 0.64. There were 17 major surgical complications, including one ECMO support period of 4 days for one patient with poor ventricular function. Six patients developed pulmonary artery stenosis and underwent a total of 15 balloon angioplasties and one stent placement to the LPA. Of the remaining eight unrepaired patients, repair is planned for six, and two are not candidates for repair.
**Anesthetic considerations**

The anesthetic management will vary according to the planned procedure, possibly including a central shunt, a staged approach to unifocalization via thoracotomy, or with a one-stage unifocalization with intracardiac repair being contemplated. The general principles for induction, maintenance, and monitoring are similar to those described earlier for TOF repair. There are several major anesthetic challenges for unifocalization via a thoracotomy, including difficulties with oxygenation and ventilation from one-lung anesthesia, hemodynamic instability, bleeding, and metabolic acidosis. In the older child, lung isolation with either a double-lumen tube or a bronchial blocker will greatly facilitate surgical exposure and minimize lung contusion from surgical retraction. Extensive intra-pulmonary and major airway bleeding from multiple vascular anastomoses will also compromise ventilation. Major blood loss should be anticipated and large-bore IV access is essential. Warming of fluids before transfusion will reduce the chance of hypothermia.

Single-stage unifocalization (with or without definitive repair) is carried out via a median sternotomy or bilateral trans-sternal thoracotomy (“clamshell” incision). As many MAPCAs as possible are mobilized, ligated, and unifocalized without CPB. As each MAPCA is ligated, the arterial saturation will decrease because a proportion of the PBF is being eliminated. At the point at which the patient nears compromise from arterial desaturation (70–75%), CPB (with moderate hypothermia and a beating heart) is initiated and the rest of the unifocalization is completed. As mentioned previously, it is vital to control as many of the MAPCAs as possible prior to initiating CPB, to prevent cerebral hypoperfusion due to increased run-off into the pulmonary circulation. After placement of a valved conduit between the RV and the MPA to restore continuity, the feasibility of VSD closure is then assessed. This is a critical step because if the VSD is closed and the “new” pulmonary vascular bed is inadequate to receive all CO, RV failure will rapidly ensue. As previously described, one approach is to obtain an intraoperative pulmonary arterial measurement with the equivalent of one indexed CO [73]. If the mean MPA pressure is less than 25 mmHg, the VSD is closed. If the RV pressure is unacceptably high after VSD closure, a fenestration can be created in the VSD connecting the RV to the new pulmonary bed, and the cardiac anesthesiologist needs to be prepared for major blood loss and replacement.

Several major problems can be anticipated post-CPB:

- **RV dysfunction** from increased afterload is treated with adequate preload, inotropic support, and ventilation adjustments/nitric oxide to reduce PVR.
- **Biventricular repair** consists of constructing a pulmonary bed using various available sources of PBF, connecting the RV to the new pulmonary bed, and closing the VSD.
- The successful post-biventricular repair requires an RV systolic pressure ≤ 50% of LV systolic pressure.
- Lung isolation can facilitate surgery, but may be difficult due to limitations with oxygenation and ventilation.
- Ventilation can be compromised from intra-pulmonary and airway bleeding from multiple anastomoses and/or lung reperfusion injury.
- RV dysfunction from increased afterload is treated with adequate preload, inotropic support, and ventilation adjustments/nitric oxide to reduce PVR.

**Summary**

Right-sided obstructive congenital heart lesions present in many different ways. Depending upon the severity of the structural anomalies, patients can present in widely divergent patterns, from the ductal-dependent, cyanotic neonate in CHF to the minimally affected young adult with mild to moderate exercise tolerance. All right-sided
obstructive CHD is characterized by the nearly universal presence of a septal defect that has the potential for right-to-left intracardiac shunt. An understanding of the physiology of the defect and effects of the proposed surgical intervention as well as the potential complications are essential for the meticulous and well planned perioperative anesthetic management of such patients.

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http://www.wiley.com/go/andropoulos/congenitalheart

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CHAPTER 24
Anesthesia for Transposition of the Great Arteries

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Introduction

Transposition of the great arteries (TGA) refers to a spectrum of conditions of discordant ventriculoarterial (VA) connections. The term TGA is most commonly used to denote concordant atrioventricular (AV) connection and discordant VA connection, where the aorta arises from the morphological right ventricle and the pulmonary artery from the morphological left ventricle. This is the most common anatomic form encountered in clinical practice and is referred to as dextro-TGA, or d-TGA. The term TGA also encompasses the hearts with discordant AV and VA connections known as congenitally corrected TGA (or ccTGA, levo- or l-TGA) and more rarely, other forms of anomalous AV connections.

Transposition of the great arteries is the second most common congenital cardiac lesion, which accounts for approximately 6% of all congenital heart defects [1]. It is frequently an isolated lesion with no other associated extracardiac anomalies. Medical and surgical advances in the past two decades have spectacularly changed the outcome of these lesions from what was a universally lethal condition into one of survivors who are expecting to lead near-normal lives.

Initial attempts at anatomical repair were associated with poor outcome, leading to the development of physiological repair by Mustard and Senning. Currently, however, the arterial switch operation (ASO) is the mainstay of management of these patients with excellent results. Surgical intervention requires the cardiac anesthesiologist to fully understand the pathophysiology, aims of treatment, surgical procedures, and postoperative consequences in order to form the perioperative management plan.

In this chapter two main subcategories of transposition will be addressed: physiologically uncorrected TGA (referred to as TGA or d-TGA) and congenitally corrected TGA (ccTGA or l-TGA).

KEY POINTS: INTRODUCTION

• TGA refers to a spectrum of conditions of discordant VA connections.
• The two main categories are physiologically uncorrected (d-TGA) and congenitally corrected (ccTGA or l-TGA).
• d-TGA is the second most common congenital cardiac lesion and accounts for approximately 6% of defects.
• The outcome of d-TGA is very good, with patients expecting to lead near-normal lives.
**Physiologically uncorrected TGA**

**Anatomy**
Physiologically uncorrected transposition of the great arteries is the most common anatomic form encountered in clinical practice and is referred to as TGA or d-TGA. In other words, the normal connections of right atrium (RA) to right ventricle (RV) and left atrium (LA) to left ventricle (LV) are preserved but there is VA discordance: the aorta arises from the RV rather than LV and the pulmonary artery (PA) from the LV (Figure 24.1).

This definition encompasses a spectrum of cardiac anomalies that can be further subdivided into either simple transposition of the great arteries or complex TGA (Figure 24.2). Approximately 75% of children present with simple TGA in which there is isolated VA (VA) discordance with either a patent foramen ovale (PFO) or patent ductus arteriosus (PDA), or both. The subgroup of TGA patients referred to as complex TGA have additional complex cardiac defects and their management and operative planning are different. Cardiac anomalies included in complex TGA are:
- Ventricular septal defect (VSD), which exists in 40% of cases with TGA
- Left ventricular outflow tract obstruction (LVOTO) in 5% of overall TGA patients
- Double outlet right ventricle and the Taussig–Bing malformation

![Figure 24.1](image1.png)

**Figure 24.1** Dextro-transposition of the great arteries (d-TGA). (A) Normal anatomy. (B) d-TGA anatomy. Ao, aorta; PA, pulmonary artery; LA, left atrium; RA, right atrium; RV, right ventricle; LV, left ventricle.

![Figure 24.2](image2.png)

**Figure 24.2** The spectrum of discordant ventriculoarterial connections that come under the “umbrella” of the term transposition of the great arteries (TGA). AV, atrioventricular; VA, ventriculoarterial; PA, pulmonary artery; VSD, ventricular septal defect; IVS, intact ventricular septum; ccTGA, congenitally corrected transposition of the great arteries; LVOTO, left ventricular outflow tract obstruction.
• Rarer abnormalities, which include TGA with VSD and coarctation of the aorta or TGA with VSD and interrupted aortic arch.

In this chapter the focus will be on the most common and important clinical subsets:
• TGA with intact ventricular septum (TGA/IVS)
• TGA with VSD including the Taussig–Bing malformation.
• TGA with LVOTO
• TGA and pulmonary vascular obstructive disease.

In the normal heart, the position of the aorta is posterior and to the right of the pulmonary trunk. There is a subpulmonary muscular infundibulum and the annulus of the aortic valve is in fibrous continuity with the mitral valve annulus [2]. In the most common manifestation of TGA, the RV connects to a right-sided and anterior aorta. There is a subaortic muscular infundibulum and the left-sided atrium connects via the mitral valve and LV to a left-sided and posterior PA. As a result there is fibrous continuity between the mitral and pulmonary valves [3,4]. This anatomical manifestation is commonly referred to as d- or dextro-TGA with the position of the aorta being anterior and to the right of the pulmonary trunk. However, in strict anatomical terms, d- or dextro-TGA describes patients who have [S,D,D] segmental anatomy, meaning situs solitus [S], d-loop ventricles [D] and d-loop great arteries [D]. This segmental approach is widely used in imaging of congenital heart disease (CHD) and consists of a three-step evaluation of the cardiac anatomy denoted by three letters. The first refers to the visceroatrial situs, the second to the right- or leftward orientation of the ventricular loop and the third to the position of the great vessels (see Chapter 4 for further discussion of nomenclature of CHD anatomy).

Although angiographically VSDs are detected in up to 30-40% of patients with TGA, only about one-third of these are hemodynamically significant [5]. The remaining 75–85% of TGA patients therefore have an intact ventricular septum (IVS). Approximately one third of the VSDs are perimembranous and another one third are outlet VSDs with malalignment. From a surgical perspective the latter are more difficult to repair. In the presence of a VSD the aorta seems to be smaller than the PA and this discrepancy in size tends to be augmented in the presence of an anterior VSD.

The Taussig–Bing heart (TBH) represents a complex subset of double outlet right ventricle (DORV) and although it is not technically a TGA, as the VA connection is double outlet, from an anatomic, physiological and management perspective, it is so similar that it is included in the TGA pathophysiology. In simple terms the TBH is a DORV with a subpulmonary VSD. The aorta originates from the RV and the PA arises from above the non-restrictive VSD. It is frequently associated with subaortic right ventricular outflow tract obstruction (RVOTO) because of hypertrophy of the infundibular septum and aortic arch obstruction. Left ventricular oxygenated blood is preferentially streamed into the PA, therefore simulating TGA physiology (see Chapter 23 for a detailed discussion of DORV).

Anatomic LVOTO can be found in approximately a third of patients with TGA and VSD, but it is rare in TGA/IVS, with an incidence of approximately 0.7%. Anatomic LVOTO can arise at the valvular or subvalvular level and be caused by many anatomical structures. Valvular obstruction might be secondary to commissural fusion, annular hypoplasia or leaflet immobility from hypertrophic tissue [6]. Subvalvular obstruction may be attributable to displacement of the conal septum, diffuse hypoplastic left ventricular outflow tract (LVOT), subvalvular membrane or the presence of accessory leaflet tissue of the AV valve. In TGA/IVS, mechanical LVOTO is uncommon but there can be functional LVOTO in the presence of high systemic right ventricular pressure, displacing the interventricular septum into the LV [7]. LVOTO limits pulmonary blood flow and therefore exacerbates the cyanosis in TGA. Chapter 22 has a further discussion of LV obstructive lesions.

Coronary artery anatomy
Coronary artery anatomy is extremely important in d-TGA patients as a successful outcome of an ASO largely depends on the transfer of the coronary arteries to the neo-aorta without narrowing or distortion. The critical importance of unrestricted aortocoronary blood flow after ASO was established during the earliest unsuccessful ASOs in the 1950s [8,9].

In the normal heart the coronary arteries arise from the aortic sinuses of Valsalva, which face the PA and are located on the anterior portion of the aorta (Figure 24.3). In TGA the coronary arteries also arise from the aortic sinuses of Valsalva, but the location of the sinuses is posterior [2]. Considerable variability exists in the origins, distribution and epicardial course of coronary artery anatomy in d-TGA. The Leiden classification system appears most commonly in surgical literature and is used in Figure 24.4 to demonstrate the frequent coronary patterns that exist in TGA [11].

Although all types of coronary anatomy are suitable for the ASO, the less common coronary patterns present potential technical difficulties for an arterial switch approach and moderately increased risk [12]. Single right coronary artery, inverted coronary artery and subtypes 7 and 8, where the coronary arteries have an intramural course, have been identified as being at increased risk [12], but recent studies have shown that with increased surgical experience, coronary artery pattern is not a risk factor for increased morbidity following the ASO [13].

KEY POINTS: ANATOMY OF D-TGA
• In d-TGA there is concordant AV connection and discordant VA connection.
• The aorta arises from the morphological RV and the PA from the morphological LV.
Pathophysiology and natural history

In the normal circulation, pulmonary and systemic blood circulates in series: deoxygenated blood from the systemic circulation enters the right heart and is delivered to the lungs via the PA. Oxygenated blood from the lungs flows via the pulmonary veins into the LA, LV and on to the body in the aorta. (Figure 24.5, left)

In TGA the anatomical variation results in the pulmonary and systemic circulations existing in parallel. This results from AV concordance – so RA to RV and LA to LV – but VA discordance – RV to aorta rather than PA, and LV to PA, rather than aorta. Oxygenated blood from the lungs drains via the pulmonary veins to the LA, then the LV but then recirculates back to the lungs in the PA. Deoxygenated blood from the body passes to the RA, then the RV and then back to the body in the aorta. Therefore deoxygenated venous blood recirculates to the body via the right side of the heart, without being oxygenated in the lungs (Figure 24.5, right). This arrangement is incompatible with life, unless a communication exists between these parallel circuits to allow inter-circulatory mixing and delivery of some oxygen to the systemic circulation. If left
Figure 24.5 Comparison of the normal circulation, which is in series, with that in transposition of the great arteries (TGA), which is in parallel. In the normal circulation (left), deoxygenated blood from the body enters the right-sided circulation, then is oxygenated by the lungs and then distributed to the body via the left side of the heart. In the transposition circulation (right), the potential sites of mixing are shown: atrial septal defect (ASD), ventricular septal defect (VSD), patent ductus arteriosus (PDA). The circulation is in parallel, so deoxygenated blood from the body enters the right side of the heart, but because of the anomalous connection, it is recirculated to the body via the aorta. Similarly, the oxygenated blood from the lungs enters the left heart but is recirculated to the lungs via the PA. This condition would be incompatible with life, if there was not any mixing of the oxygenated and deoxygenated blood. RA, right atrium; RV, right ventricle; PA, pulmonary artery.

Untreated then death from hypoxia and congestive heart failure (CHF) will occur in 90% of patients within the first year of life.

Inter-circulatory mixing is vital for survival in children with TGA and the amount of mixing greatly influences the hemoglobin oxygen saturation and the severity of the clinical picture. Mixing can occur at several levels and these can be divided into intra and extra-cardiac. Potential intracardiac sites for mixing are at the atrial level (ASD and PFO) or the ventricular level (VSD). Extracardiac sites include intra-arterial mixing at the level of the great arteries through the PDA. It is the effectiveness of mixing that determines hemoglobin oxygen saturation and therefore the severity of the clinical presentation. The effectiveness of mixing is affected by many factors that can be thought of as anatomical and physiological. The number, site, and position of the inter-circulatory communications are important [14,15]. Having one unrestrictive communication is better than multiple restrictive ones and also certain positions can be less favorable than others. Physiological factors also influence the degree and effectiveness of mixing. At the level of the anatomical communication, flow can be impaired if, for example, ventricular compliance is reduced and systemic and pulmonary vascular resistances (SVR, PVR) are increased. Generally, mixing at the level of the atrial septum is most effective because the left atrial pressure (LAP) is consistently higher than the right atrial pressure, and thus the direction of flow is left-to-right throughout the cardiac cycle (highly oxygenated pulmonary venous blood to desaturated systemic venous blood), therefore increasing RV oxygen and thus aortic saturation. Mixing at ventricular septal or PDA level is not as effective, because of more bidirectional shunting of desaturated blood (aorta to PA via PDA, RV to LV via VSD). This is the physiologic reason that balloon atrial septostomy (see below) is pursued for cyanotic d-TGA patients. The efficiency of mixing is further influenced by total pulmonary blood flow (Qp) [15]. Pulmonary blood flow is reduced, for example, if there is subpulmonary stenosis or pulmonary vascular occlusive disease and therefore the degree of mixing is also reduced. A decrease in pulmonary blood flow caused by a decrease in overall cardiac output (e.g., hypovolemia, depressed myocardial contractility from volatile anesthetics) leads to increasing cyanosis.

If by effective blood flow we define the proportion of blood flow that is physiological (i.e., systemic blood which has the capacity to deliver tissue oxygenation and pulmonary blood that delivers deoxygenated blood to the lungs), then inter-circulatory mixing produces effective systemic and pulmonary blood flow. In TGA, because of the systemic and pulmonary circulations existing in parallel, this effective blood flow is only a small proportion of the recirculated blood which makes up the largest proportion of systemic and pulmonary blood flow. The greater the volume of the effective systemic blood flow relative to the recirculated flow, the greater the arterial oxygen saturation. As noted earlier, in clinical terms the amount of mixing at the atrial level seems to be the most important determinant of oxygen saturation and therefore of severity of clinical presentation.

The commonest presentation of infants with TGA is cyanosis, but the degree of this varies amongst the different subsets of TGA and is dependent on the sites and efficiency of mixing. Newborns with TGA/IVS with a small PDA or PFO have severe cyanosis on the first day of life that can lead to acidosis and cardiovascular collapse. Those with TGA/IVS with a large PDA or PFO/ASD or TGA with VSD, have better mixing and thus higher PaO₂, but they also have a greater tendency to develop CHF.
TGA and pulmonary vascular occlusive disease

Children with TGA are at particular risk of developing pulmonary vascular occlusive disease compared with other congenital heart lesions, especially in TGA with VSD. Most factors that are thought to contribute to the disease process of pulmonary vascular occlusive disease are present in these patients: hypoxemia, polycythemia, high pulmonary blood flow, and high PA pressure [5]. Pulmonary venous congestion or occlusion increases PVR and will lead to pulmonary hypertension, which decreases pulmonary blood flow, reducing inter-circulatory mixing and therefore worsening systemic hypoxemia. It is important for surgical correction to occur before the development of irreversible pulmonary vascular occlusive disease, as advanced pulmonary hypertension will reduce the number of therapeutic surgical options available to the patient. Cardiac catheterization establishes the degree of increased pulmonary arteriolar resistance, and surgical planning is based on that data. However, in the modern era, this is usually not required as surgery is undertaken early.

KEY POINTS: PATHOPHYSIOLOGY AND NATURAL HISTORY

- In d-TGA the pulmonary and systemic circulations exist in parallel.
- Deoxygenated venous blood recirculates to the body through the right side of the heart, without being oxygenated in the lungs, and oxygenated blood recirculates between the lungs and the left side of the heart.
- Inter-circulatory mixing is vital for survival in children with d-TGA.
- Mixing can occur through a PFO, ASD, VSD, or PDA.
- Atrial level mixing is the most effective way to increase oxygenation.
- The amount and adequacy of mixing influence the oxygen saturation and severity of presentation.

Clinical presentation and preoperative management

Transposition of the great arteries usually presents as a spectrum of cyanosis and/or cardiac failure depending on the associated anatomical features. Cyanosis is more pronounced in the absence of adequate inter-circulatory mixing and CHF is more common where there is a large amount of mixing and therefore increased pulmonary blood flow. Following birth, resuscitation and stabilization with prostaglandin E$_1$ (PGE$_1$), urgent balloon atrial septostomy (BAS) and mechanical ventilation may be required. In general terms, unless the above measures fail, the concept of emergency operation for TGA has been replaced by resuscitation and stabilization in preparation of semi elective ASO. Risk factors for preoperative mortality include the presence of restrictive PFO or ASD, persistent pulmonary hypertension, low birth weight and prematurity [16–18].

TGA with IVS

In TGA/IVS, inter-circulatory mixing occurs at two main sites: PFO and PDA and the degree of mixing depends on the size of the atrial communication (PFO) and the patency of the PDA. In the presence of a non-restrictive atrial communication and low PVR, blood shunts from the aorta to the PA via the PDA and then from the LA to the RA across the atrial septum, resulting in a higher proportion of effective blood flow through the systemic and pulmonary circulations. On the other hand, in the presence of a restrictive atrial communication, the LA pressure increases. When PVR is high, and the pressure in the PA is higher than that in the aorta, shunting across the PDA is predominantly from the PA to aorta. In this situation the pre-ductal arterial saturations (right arm) will be lower than the post-ductal arterial saturations (legs). This physiology is associated with poor mixing and therefore low effective blood flow and hypoxemia.

It is worth mentioning that although the presence and patency of the PDA can improve arterial oxygenation, there is a fine balance between achieving arterial oxygen saturation and developing pulmonary venous congestion, especially in smaller infants without adequate inter-arterial mixing. These children are at risk of preoperative or sudden death at birth, following PFO closure [16,19]. The majority of neonates with TGA/IVS are severely cyanosed, with arterial saturations of lower than 60% [20], with a proportion of them having a PaO$_2$ <25 mmHg. This results from severely reduced effective blood flow into both the systemic and pulmonary circulation. Poor oxygen delivery to the tissues results in worsening metabolic acidosis and hypercarbia. Measures to increase the effective pulmonary and systemic circulation include the following: PGE$_1$ administration for PDA dilatation and maintenance of patency, controlled ventilation, and BAS done as an urgent procedure.

Prostaglandin E$_1$ causes vasodilatation by relaxing the smooth muscle of the PDA and maintaining its patency. It is effective in increasing PaO$_2$ and improving tissue oxygen delivery in the presence of an unrestricted atrial communication. The efficacy of prostaglandin infusion in TGA/IVS is also influenced by the PVR. If the PVR is high then total blood flow through the lungs will be reduced. These patients may require sedation, intubation, muscle relaxation, and mechanical ventilation in order to control PVR, increase Qp, and improve ventilation/perfusion mismatch. This is achieved by controlling the PaCO$_2$ and inducing a respiratory alkalosis, which results in PVR reduction. In addition, the inspired oxygen concentration can be carefully controlled. Sedation and muscle relaxation further decrease the systemic metabolic demands.

If prostaglandin infusion does not improve oxygenation and/or the atrial communication is restrictive, then a BAS is performed as an emergency. Depending on the urgency of the procedure, a BAS can be performed using either echocardiography or angiography. The former is usually done as an emergency in intensive care and the latter in the more controlled environment of the cardiac catheterization.
laboratory. The aim of the procedure is to enlarge the atrial communication, improve inter-atrial mixing and increase the effective flow through the systemic and pulmonary circulation. It also relieves pulmonary venous congestion and decompresses the LV [21]. The procedure was developed in the mid-1960s by Rashkind and Miller [22]. A balloon septostomy catheter is introduced percutaneously, usually via the femoral vein (the umbilical vein can also be used), into the RA. It is navigated through the PFO into the LA where the balloon tip is inflated and pulled downward to tear the inferior aspect of the foramen ovale and enlarge the ASD [22]. Most neonates improve after BAS because of improved mixing and arterial oxygen saturation and can therefore be extubated and begin oral feeding on the ward. The prostaglandin infusion can usually be stopped. Poor results after BAS are highly suggestive of pulmonary hypertension.

In the majority of cases, these therapeutic maneuvers improve arterial oxygenation and achieve stability before a definitive surgical repair is undertaken. In the rare instance where these maneuvers fail to improve the condition of the baby, urgent surgical correction may be undertaken. Extracorporeal membrane oxygenation (ECMO) can be considered as a means of improving both tissue oxygenation and end-organ perfusion, while reducing lactic acidosis.

With an IVS, pressure in the LV decreases as PVR decreases physiologically over the first several weeks of life; the LV undergoes partial involution in terms of muscle mass and ability to contract efficiently and deliver a normal stroke volume against the systemic resistance of the aorta after the ASO. Therefore, although there is not a set age limit to undergo ASO, d-TGA/IVS patients are usually operated upon in the first several weeks of life (see later).

**TGA with VSD, with or without LVOTO**

Infants with TGA and VSD have increased pulmonary blood flow and a large degree of inter-circulatory mixing and are therefore less likely to develop cyanosis. They often have mixing both at the atrial (LA to RA) and ventricular levels (RV to LV) and usually manifest symptoms of CHF. Although these symptoms can occur in the early neonatal period, they usually present in the first few weeks of life when PVR is at its lowest postnatally. These patients are commonly stable enough not to require immediate intervention, but depending on the clinical presentation, they may benefit from diuretics, vasodilators, and low-dose inotropic support before the surgical procedure.

The presence of an interventricular communication exposes the LV to systemic pressures and therefore prevents LV involution, in contrast to TGA/IVS. These infants are candidates for the ASO before intractable cardiac failure or pulmonary vascular occlusive disease occur. In the presence of advanced pulmonary hypertension, VSD closure has a high mortality rate due to the resultant LV dysfunction, so ASO with either fenestrated closure of the VSD or without closure of the VSD is performed.

In the presence of LVOTO, pulmonary blood flow and the extent of inter-arterial mixing are low. The main clinical feature is cyanosis and hypoxemia, the degree of which depends on the extent of the obstruction. In severe LVOTO, poor oxygen delivery to the tissues results in worsening metabolic acidosis and hypercarbia and the child might need to be resuscitated with a PGE$_1$ infusion and mechanical ventilation.

**Diagnostic features**

There are typically no characteristic features on clinical examination, chest radiographs, or electrocardiography that differentiate TGA from other cause of neonatal cyanosis. The main diagnostic modality is echocardiography, which establishes the diagnosis and identifies the presence of other associated anatomical defects. With the evolution of fetal echocardiography, most diagnoses of TGA are now likely to occur antenatally. As a result, associated cardiac defects can be established prenatally and a preliminary management plan can be formed aiming at postnatal stabilization before a more definitive surgical correction takes place. A detailed echocardiogram is repeated at birth to obtain further anatomical information, including coronary artery anatomy, and to aid preoperative management and surgical planning.

Cardiac catheterization is not routinely performed unless it is in conjunction with BAS, when ECHO cannot establish coronary artery anatomy, or to quantify pulmonary vascular occlusive disease and PVR in the older child.

Some additional associated findings on electrocardiography and chest radiography are as follows:

- In TGA/IVS: The main findings on ECG are a right axis deviation and right ventricular hypertrophy, and chest radiograph shows an “egg-shaped” heart, narrow superior mediastinum and increased pulmonary vascular markings
- In TGA and VSD: ECG shows signs of right axis deviation, left and right ventricular hypertrophy, and chest X-ray shows a large cardiac silhouette and increased pulmonary vascular markings.

**KEY POINTS: CLINICAL PRESENTATION AND PREOPERATIVE MANAGEMENT**

- TGA usually presents as a spectrum of cyanosis and/or cardiac failure depending on anatomy and degree of mixing.
- Diagnosis is usually made prenatally with fetal echocardiography.
- Stabilization with PGE$_1$, urgent BAS, and mechanical ventilation may be required.
- PGE$_1$ maintains the PDA and is effective at increasing PaO$_2$ in most patients with relatively unrestricted atrial communication.
- If PGE$_1$ does not improve oxygenation, a BAS is performed.
Surgical options
The earliest unsuccessful attempts of the ASO date back to 1954 by William Mustard, who performed the switch operation on seven patients, in whom only the left coronary artery was translocated to the ascending aorta. The 100% mortality rate led to it being abandoned in favor of the atrial switch operation. The first successful atrial switch operation was performed by Ake Senning in 1958 and was later modified by Mustard. The atrial switch procedures decreased the mortality of the condition, but the unsatisfactory longer-term complications continued to make the arterial switch procedure appealing. During these early pioneering years, it was recognized that an unprepared LV in the presence of IVS would fail and that the variability of coronary anatomy is important in the development of the surgical technique. Adib Jatene performed his first successful ASO in 1975 in São Paulo, Brazil, for a TGA with VSD and its success was replicated in the following years in this subgroup of patients. An important milestone in the evolution of the procedure, which made it appealing and applicable to a wider patient population, was proposed by Lecompte in 1982. The Lecompte maneuver describes the placement of the distal neo-aorta posteriorly to lie behind the PA bifurcation, obliterating the need of a bridging conduit. By 1984, Castenada reported a small series of primary ASOs for simple TGA with reasonable mortality rate. The ASO is now the mainstay of management in various subsets of TGA with very low mortality rates, excellent immediate postoperative outcomes and good long-term results.

Indications and timing of the ASO
The ASO was first successfully described, performed, and replicated in TGA with VSD, but currently there is near-universal acceptance of the ASO as the preferred treatment of most forms of TGA (Figure 24.6). One of the most important contributions to this development has been from the Boston group in 1989 [23], who quantified the very rapid increase of LV mass in neonates after PA banding. It became apparent that adequate retraining of the LV to function to systemic pressures could occur in as little as a week, therefore making the ASO applicable to older neonates. Current indications for ASO include both TGA patients and children with more complex cardiac pathology.

Some examples include the following:
- Simple TGA
- TGA with VSD or TBH
- TGA with severe subaortic stenosis, coarctation with severe arch hypoplasia
- Double inlet left ventricle
- RV dysfunction and tricuspid insufficiency after Mustard or Senning operation.

Optimal timing of ASO depends on the associated anatomical features, with the LV pressure at the time of presentation being one of the key considerations. Left ventricular mass is vital to ensuring the success of the procedure and therefore patient selection and timing are important. A successful primary ASO repair is usually performed in the first 2–3 weeks of life when there is adequate LV mass to support the systemic circulation. It can be performed as a staged procedure for neonates in whom surgery cannot be performed in the early stages of life, because of low birth weight, prematurity or sepsis, for example. In this situation, the LV is “trained” to increase its muscle mass, in order for it to be able to function when exposed to systemic pressures. This is achieved by increasing the LV afterload by placing a band around the PA. The tightness of the pulmonary artery band (PAB) is

Figure 24.6 The arterial switch operation (ASO). Schematic representation of d-transposition of the great arteries anatomy before (A) and after (B) the ASO. Ao, aorta; PA, pulmonary artery; LA, left atrium; RA, right atrium; RV, right ventricle; LV, left ventricle.
adjusted to produce pressure that is half to two-thirds of that of the systemic ventricle.

In contrast to the normal heart, in TGA the LV mass involutes as the PVR decreases postnatailly, resulting in a relatively thin-walled LV. In TGA/IVS where there is postnatal involution of the LV, there is concern in the older infant that the ventricle might not function well when exposed to systemic pressure and resistance, putting them at risk for low cardiac output state and LV failure following an ASO. Therefore the optimal timing of the ASO in these patients is thought to be in the first 2–3 weeks of age. This is to prevent involution of the LV, which has been functioning as the low-pressure pulmonary ventricle. There is a small proportion of infants where adequate oxygenation cannot be maintained despite BAS and PGE infusion and they will require an earlier operation. In infants who present later or where there are other concurrent medical problems such as sepsis or necrotizing enterocolitis and an ASO cannot be performed in the above timeline, preliminary PA banding to “train” the LV to tolerate higher pressures and increase LV mass might be necessary prior to the ASO.

In the subsets of patients where the LV is exposed to systemic pressures, such as LVOTO, a large VSD or PDA may maintain high LV mass after birth, preventing LV involution well beyond the age of 2–3 weeks. In these patients there is less urgency to perform the surgery and this is usually done in the first 6 weeks of life. The operation might be performed at 6–8 weeks if the infant is stable and thriving. In reality, though, they are operated on within the first month of life and are candidates for the arterial switch procedure before intractable cardiac failure or pulmonary vascular occlusive disease occur.

**TGA/IVS and LVOTO**

In patients with TGA and LVOTO, the decision on whether to perform the ASO is made on an individual basis and depends on the nature of the LVOTO. If the obstruction is dynamic rather than anatomical, then the ASO is indicated, given that normal LV/RV pressure ratio will be restored following the repair and therefore the dynamic nature of the LVOTO will be fully reversed and there will be no residual LVOTO gradient.

In the case of anatomical obstruction, management depends on the underlying cause of the LVOTO. ASO is generally thought to be appropriate when complete relief or near-complete relief is to be expected. Careful assessment of the individual case is of the essence. It may be preferable for the patient to undergo direct relief of LVOTO and a concomitant ASO rather than other types of surgical repair. Recent data have demonstrated that pulmonary valve and LVOTO abnormalities are not a contraindication to the arterial switch procedure and the left ventricular to PA gradient alone should not be the basis to judge the severity of the obstruction. Residual gradients in the LVOTO have been shown to be well tolerated clinically up to 10 years after the ASO [5,24,25]. In the presence of severe fixed LVOTO, if the surgical relief is likely to be difficult, then different treatment strategies such as the Rastelli or REV (reparation a l’étage ventriculaire) procedure, might be required. Both of these procedures involve the creation of an LV-to-aorta patch tunnel to close the VSD and correct blood flow physiologically; and do not involve an arterial switch or coronary translocation. The Rastelli procedure adds an RV-to-PA conduit for pulmonary blood flow, whereas the REV procedure anastomoses the main PA directly to the RV, and RVOT infundibular resection is extensive to prevent RVOTO. Infants with TGA and severe arch obstruction or Taussig–Bing anomaly are suitable for the ASO and typically require urgent operation after resuscitation with PGE, and mechanical ventilation. Arch obstruction is more common in patients with complex intracardiac anatomy and either consists of coarctation with hypoplastic arch or interruption. In both cases, a one-stage operation is usually undertaken [26].

**Surgical technique of ASO**

The ASO is performed through a median sternotomy on cardiopulmonary bypass (CPB). For simple TGA it is possible to utilize a single venous cannula placed through the right atrial appendage, although some surgeons use bicaval cannulation for any neonate. For complex cases involving intracardiac surgery, the cavae are always cannulated separately. When CPB is established, the ductus arteriosus is divided, the ascending aorta is clamped, and cardioplegia is administered. The ascending aorta is transected above the commissures and the left and right coronary arteries are excised with a large cuff of aortic tissue. The MPA is transected and the coronary arteries are reimplanted into the remaining cuff of the PA which will become the neo-aorta (Figure 24.7) The Lecompte maneuver is performed so that the ascending aorta is moved to lie behind the bifurcation of the PA (Figure 24.8). The aortic explant sites are repaired with a pericardial patch and the aorta is anastomosed to the LVOT and the PA is sutured to the RV outflow. The ASD is usually closed by direct suture. In patients with a VSD, this would be closed with a pericardial patch. In children with the TBH, the VSD is closed with a patch placed diagonally in such a way so as to achieve continuity of the LV with the neo-aorta, while the neo-PA remains connected to the RV. With the heart repaired, a pressure monitoring catheter is placed in the left atrial appendage, and in some centers one is also placed in the neo-main PA [26]. Once the aortic cross-clamp is removed, the myocardium is carefully observed for perfusion, and LAP is closely monitored (Figure 24.9). Ischemia of the myocardium is reflected by lack of reactive hyperemia or a rise in LAP, even before the electrocardiographic changes become apparent. Rises of LAP above 10 mmHg require careful re-examination of the myocardium and coronary vessels to ensure adequate coronary flow. During rewarming, the aortic sinus defect is repaired, the anastomosis is completed and temporary atrial and ventricular pacing wires are attached. Modified ultrafiltration follows CPB discontinuation in many centers and it is during this period that hemodynamics are optimized.
Other surgical procedures
Rastelli procedure
The Rastelli procedure is performed on hypothermic bypass and is used as a method of anatomically correcting TGA with VSD and LVOTO (Figure 24.10). A right ventriculotomy is performed and the VSD is closed with a patch placed diagonally in such a way that the LV is in continuity with the aorta. The PA is ligated at the level of the pulmonary valve and an RV-to-PA conduit is placed. The conduit can be an aortic or pulmonary homograft with a polytetrafluoroethylene graft extension. It therefore achieves LV to aortic and RV to PA continuity, while bypassing the LVOTO. In the past these patients had a systemic-to-pulmonary artery shunt inserted in the neonatal period and subsequently had the Rastelli operation and takedown of shunt at approximately 2–3 years of age. Currently the Rastelli procedure is performed as a primary procedure in the first few months of life.
Common postoperative concerns with the Rastelli procedure

The main immediate postoperative concerns following the Rastelli procedure are the presence of a residual VSD, arrhythmias (mainly heart block and junctional ectopic tachycardias) and low cardiac output state, especially in patients who have required long VSD patches or VSD enlargement.

Senning and Mustard Procedures

These procedures, which are also known as atrial switch procedures, were the mainstay of surgical correction until the mid-1980s and have now been largely replaced by the ASO. The Senning procedure was developed by the Swedish surgeon Ake Senning in 1958, an operation that provides physiologic correction of the TGA. Using autologous atrial flaps, an intracardiac baffle is created which redirects systemic venous flow to the LV and pulmonary venous flow to the RV. The Mustard procedure was developed by the Canadian surgeon William Mustard in 1964 and is a modification of the Senning procedure. In this operation the interatrial septum is excised to create a large ASD and a baffle, made of either autologous pericardium or synthetic material, is used to redirect systemic and pulmonary venous blood flow to the LV and RV, respectively (Figures 24.11 and 24.12) The Mustard procedure has also been used as a palliative procedure (with non-closure or fenestrated closure of VSD) in patients with TGA and VSD with advanced pulmonary vascular occlusive disease. The aim of the procedure is to improve arterial oxygenation by facilitating inter-circulatory mixing; however, it does not reverse or decelerate pulmonary vascular occlusive disease progression.

Early results were good for both procedures with the most common late complications being RV failure (estimated to be approximately 10% in the first decade), baffle issues such as leak or stenosis, and intractable atrial arrhythmias [29–32]. Common rhythm disturbances included sick sinus syndrome, because of scarring of the sinus node, or atrial flutter because of scarring around the baffle sutures.

The atrial switch operations are rarely offered nowadays for d-TGA unless the patient presents late, rendering the ASO difficult because of LV involution. Even if that is the case, quite often a PA band is placed for several weeks or months to strengthen the LV to the extent that an ASO is possible.

Systemic-to-pulmonary artery shunts

These are considered in patients with d-TGA, VSD and severe LVOTO, where the pulmonary blood flow is low.
Figure 24.10 Schematic representation of the Rastelli procedure for repair of transposition of the great arteries with ventricular septal defect (VSD) and left ventricular outflow tract obstruction (LVOTO). (A) Baffle closure of the VSD with a patch redirecting left ventricular outflow across the aortic valve. (B) In the presence of LVOTO, the proximal pulmonary artery (PA) is ligated and a valved conduit is placed from the right ventricle to the main PA.

Figure 24.11 Postoperative specimen of transposition of the great arteries after the Mustard operation. The tomographic cut is comparable to an apical four-chamber echocardiographic projection. The patch within the atrium (black arrowheads) directs pulmonary venous blood to the tricuspid valve and into the right ventricle (RV). LA, left atrium; PV, pulmonary vein; RA, right atrium; VS, ventricular septum. (Source: Warnes [28]. Reproduced with permission of Lippincott, Williams & Wilkins.)

and the inter-arterial mixing limited. The aim of the procedure is to increase pulmonary blood flow. In our center a modified Blalock–Taussig shunt (mBTS) is used if children are too young to be considered for the Rastelli procedure. This involves a shunt creation between the subclavian artery and the corresponding side branch of the PA.

**KEY POINTS: SURGICAL OPTIONS**

- The most common procedure for d-TGA is the ASO; others include the Rastelli procedure and (rarely) the atrial switch.
- The atrial switch (Senning and Mustard) were common until the mid-1980s and are now completely replaced by the ASO.
- Indications for ASO include both simple and more complex d-TGA anatomy.
- Left ventricular mass involutes in d-TGA/IVS as PVR decreases postnatally.
- ASO repair is usually performed in the first 2–3 weeks of life.
- The ascending aorta is transected and the coronary arteries are excised and reimplanted into the PA; the aorta is anastomosed to the pulmonary valve, which becomes the neo-aortic valve.
- The PA is transected and reanastomosed to the aortic valve, and the defects where the coronaries were removed are patched.

**Anesthetic considerations and perioperative management**

The importance of an anesthetic team with expertise in newborn open heart surgery is vital. It is essential for the anesthesiologist to have a detailed understanding of the pathophysiology of the TGA lesion, other associated anomalies, the overall condition of the child and any
interventions that have been undertaken to stabilize the child.

Preoperative assessment
The preoperative assessment in children with congenital heart defects is a multidisciplinary assessment involving cardiologists, surgeons, anesthesiologists, perfusionists and intensive care physicians, to name a few. This information will be collated from a detailed history, physical examination, review of the imaging and laboratory results. In CHD the majority of this information will be obtained from the medical records. In our center, as in others, joint cardiac conferences are held prior to the procedure where the cardiac defect and options for treatment are discussed. The report produced can be valuable in assessing the child and gaining an overall understanding of the pathophysiology and medical course thus far and also the specific type of operation for which the child is scheduled.

The preoperative anesthetic evaluation in children with TGA should focus and be tailored to obtaining the following information:

- The presence of associated cardiac anomalies, e.g., VSD or LVOTO or other anomalies.
- The adequacy of inter-circulatory mixing – if there is an atrial communication and whether this provides adequate mixing, i.e. restrictive or unrestrictive.
- Whether a BAS has been done and with what result.
- Whether the circulation is prostaglandin-dependent as this will need to be continued to ensure adequate mixing until CPB. The dose of the infusion should be noted as well as the presence of any potential side-effects, especially if higher doses are being used. These include fever, apneas, vasodilatation, hypotension, decreased intravascular volume, hypertonicity and central nervous system (CNS) excitability.
- Ventricular size and function.
- Coronary anatomy.
- Detailed assessment of the cardiorespiratory status should include assessment of the presence of arrhythmias, level of inotropic support and cyanosis as well as looking for symptoms and signs of congestive cardiac failure and pulmonary overcirculation.

Anesthetic goals
The following points provide a quick guide to the primary anesthetic goals for the ASO:
- Maintenance of ductal patency with PGE₁ infusion in ductal-dependent patients.
- Maintenance of cardiac output by maintaining heart rate, contractility and preload is important. Decreases in cardiac output will decrease systemic arterial saturation.
- The PVR needs to remain lower than the SVR in order to ensure effective blood flow through the lungs. If the PVR is increased then the resultant decrease in pulmonary blood flow reduces inter-circulatory mixing. Simple first-line interventions rely mainly on ventilatory control: increase of FiO₂ and elective hyperventilation to achieve a moderate metabolic alkalosis should effectively reduce PVR. Avoidance of acidemia, hypothermia, and hypoxemia is also important in avoiding increases of PVR.
• The SVR should be kept high in relation to the PVR to avoid increased recirculation of systemic venous blood and further decrease in arterial saturations.
• In patients with TGA and VSD who have symptoms of LV overload and CHF, ventilatory interventions to reduce PVR only produce a small improvement in arterial saturation at the expense of systemic perfusion and are therefore unnecessary.

Children with cyanotic cardiac defects are prone to coagulopathies that are multifactorial in nature and are also exacerbated by post-bypass coagulopathy. Availability of blood and blood products is therefore very important. Although coagulation and bleeding will be examined in more detailed in the following sections, a brief summary is helpful here. Chronic cyanosis triggers increased erythropoiesis, increased circulating blood volume and vasodilation to increase oxygen delivery to the tissues and compensate for chronic hypoxemia. Polycythemia results in increased blood viscosity and increases both PVR and SVR. Interestingly, the increase in PVR is greater than the increase in SVR, further decreasing pulmonary blood flow in children who already have compromised blood flow. To avoid cerebral, pulmonary and renal thrombosis as a result of increased viscosity, adequate hydration should be ensured by either avoiding long periods without oral intake or providing intravenous hydration.

**KEY POINTS: ANESTHETIC GOALS**

- Maintain the PDA with PGE₁ in the duct-dependent circulation.
- Avoid increases in PVR and reductions in SVR to ensure adequate pulmonary blood flow and avoidance of recirculation of pulmonary venous blood.
- After CPB, the LAP needs to be low while maintaining adequate cardiac output.
- Pulmonary hypertension should be avoided.
- Intravascular volume administration should be very cautious, because even a small amount of volume can increase LAP dramatically.

**Anesthetic intraoperative management**

Induction of anesthesia can be inhalational or intravenous and should be tailored to the child. Non-invasive monitoring such as pulse oximetry, ECG and non-invasive blood pressure monitoring should ideally be attached prior to induction, although the difficulty in always achieving this has been recognized. The most commonly used inhalational agent for induction is sevoflurane and it is worth noting that in cyanosed children, induction of anesthesia will be slower. A balanced opioid-based anesthetic that includes an inhalational agent is preferred for maintenance of anesthesia, as it is thought to better control the hemodynamic and stress responses to cardiac surgery [24,34]. A number of different opioids can be used. In the UK, fentanyl is one of the opioids commonly used. Dosing varies widely between anesthetists but total doses can be anywhere from 30 to 100 μg/kg. Another agent that is used intraoperatively in some centers and has gained popularity in pediatric intensive care units is dexmedetomidine which is an α₂ agonist. It can be used intraoperatively as an adjunct to other sedative-analgesic regimes, due to its minimal effects on cardiovascular function. Dexmedetomidine is examined in more detail under postoperative sedation in the next section. A commonly used muscle relaxant is pancuronium at a dose of 0.1 mg/kg, which is administered in conjunction with the opioid to avoid bradycardia. However, particularly as pancuronium is not available any longer in many parts of the world, many other muscle relaxants can be used.

Following intubation, which is usually nasal, invasive arterial and central line placement is required. Preferred sites for arterial line placement are the radial, femoral, or axillary arteries in very small children. The brachial artery is generally avoided as it is an end artery. In the rare occasion where arterial cannulation proves to be difficult, the surgeons can place a catheter in the internal mammary artery following sternotomy to allow monitoring of invasive blood pressures and sample-taking or, alternatively, perform a cut-down onto a peripheral artery; however, this is very seldom necessary. Similarly, a central venous pressure catheter can be inserted into either the internal jugular or the femoral vein. If VSD closure and bicaval cannulation for CPB is required, a femoral central venous catheter might be preferable, as the presence of a venous catheter in the superior vena cava may make superior vena cava cannulation for bypass more difficult.

In our unit, central venous lines are routinely placed using ultrasound guidance and many anesthesiologists would also routinely use ultrasound guidance to place arterial lines. Ultrasound-guided placement of invasive lines improves patient safety and diminishes the risk of any associated complications of line insertion. It also can be a useful adjunct in verifying catheter position [35-39]. Chapter 10 has an extensive discussion of ultrasound-guided vascular access.

Following invasive monitoring placement, nasopharyngeal and peripheral skin temperature probes are attached for monitoring as core temperature is tightly regulated during CPB. The gastric contents are suctioned via a nasogastric tube that will remain in situ postoperatively in intensive care and a urinary catheter is inserted which also remains in place for postoperative management.

The benefit of echocardiography in cardiac assessment immediately after repair while the chest is open is indisputable and used in most centers. However, whether this is performed by the use of routine transesophageal echocardiography (TEE) or epicardial echocardiography depends on the unit involved. In our unit we would not routinely place a TEE probe because the patient’s size is too small in relation to our smallest TEE probe. Some centers with smaller probes would use TEE routinely. There is benefit in the use of TEE immediately after repair.
for the assessment of adequate de-airing, myocardial function, detection of any residual defects, evaluation of neo-aortic valve regurgitation and adequacy of coronary anastomosis. However, the incidence of complications is higher in neonates and the TEE probe placement can be challenging. It can cause an increase in peak airway pressures, resulting in problems with ventilation or hemodynamic compromise from left atrial compression as well as more serious complications such as esophageal laceration or perforation.

Antibiotics and corticosteroids
Prophylactic antibiotics are administered before skin incision and are governed by local policies.

A heightened inflammatory response during bypass has been postulated to affect cardiac function, leading to postoperative hemodynamic instability by causing fluid shifts and contributing to low cardiac output state [40]. As a result there is widespread empirical use of steroids as prophylactic anti-inflammatory therapy in pediatric cardiac surgery [40]. Neonates are the most susceptible group to the perioperative stress of open-heart surgery and have a reduced response to inotropic agents compared with the adult heart [41]. The results in present and earlier studies suggest that a single dose of glucocorticoid produces only a transient or no significant effect on cardioprotection or clinical outcome in neonates, no difference in low cardiac output syndrome incidence and no difference in postoperative mortality [41,42]. Despite a reduction in preoperative cytokine levels, the biochemical reduction seems not to correspond with clinical effects and it does not persist postoperatively either [41]. Furthermore, some studies have demonstrated that the use of steroids increases the length of intensive care stay and is associated with greater use of insulin from the resultant hyperglycemia, especially if used in higher doses [43]. Steroids are not routinely used in our centre as a means of reducing the proinflammatory state of surgery and CPB.

Further non-invasive monitoring: neuromonitoring and the use of near-infrared spectroscopy
There is increased interest in intraoperative neuroprotection in children who have undergone surgical repair or palliation of their congenital heart defect. The reported incidence of neurological complications after pediatric cardiac surgery ranges from 2% to 25% [44,45]. In general, mechanisms of central nervous system injury in children undergoing cardiac surgery are multifactorial and include preoperative brain malformations, perioperative hypoxia–ischemia, emboli, low cardiac output states, the sequelae of CPB and deep hypothermic arrest [46–48]. Neonatal CPB with or without modifications such as deep hypothermic circulatory arrest is a clear risk factor for neurologic complications and characteristic changes in cerebral oxygenation occur during CPB [44,49,50]. This has resulted in the introduction of real-time neurophysiologic monitoring to assess the adequacy of blood flow and oxygen delivery to the brain. Near-infrared spectroscopy is a non-invasive continuous monitoring tool that has been validated as a measure of regional oxyhemoglobin saturation and can assist in the detection of low flow states. The cerebral oximeter probe is placed on the forehead below the hairline [44]. Most devices use two to four wavelengths of near-infrared light at 700–1000 nm, where the iron–porphyrin complexes of oxygenated and deoxygenated hemoglobin have distinct absorption spectra [44,47,51]. Commercially available devices measure the concentrations of oxyhemoglobin and deoxyhemoglobin and determine the cerebral regional oxygen saturation (rSO₂). Most studies have demonstrated the benefit of neurophysiologic monitoring during CPB [52] in terms of outcome and further neurodevelopment, but there is limited knowledge about how to manage CPB in terms of flow increase and decrease according to cerebral oximetry values. Chapter 11 presents an extensive discussion of neurological monitoring and outcomes.

Management of anticoagulation
Cardiopulmonary bypass techniques are unique to each center, but adequate anticoagulation is vital for the maintenance of CPB. Prior to commencing CPB, the surgeons direct the timing of heparin administration to traditionally aim for activated clotting time (ACT) > 350 seconds or three times baseline. The doses of heparin given to children have been extrapolated from weight-based adult protocols [53,54], not taking into consideration the fact that children have higher metabolic rates and larger blood volume to body weight ratio than adults [53,55–57]. Although these protocols appear to be successful in preventing macroscopic clot formation while on CPB, they do not ensure inhibition of the clotting system on a molecular level. Antithrombin inhibits the procoagulation effects of thrombin. The affinity of antithrombin to thrombin and its enzymatic inhibition is increased by binding of antithrombin with the heparin. However, there are small amounts of thrombin bound to fibrin, the injured vessel wall, or the CPB circuit, which are prevented from interaction with the antithrombin III–heparin complex [58]. This prevention of inhibition renders some of the thrombin enzymatically active and might therefore lead to clot formation in the immediate post-bypass period or to activation of the coagulation system during bypass, causing microthrombi formation and depletion of the core elements of the coagulation system, resulting in a more severe coagulopathy post-bypass. Excessive anticoagulation, on the other hand, may place patients at risk of postoperative bleeding complications [54,59,60].

The primary monitor of heparin-induced anticoagulation during CPB is the ACT. ACT is a measure of whole blood coagulation status and is often affected by other factors other than heparin. There is well-documented evidence that the ACT value has serious limitations as a monitor of heparin-induced anticoagulation during CPB. Several studies have shown a poor correlation between ACT values and plasma heparin concentrations in both
adult and pediatric patients undergoing CPB [61,62]. Hypothermia, hemodilution, and impaired platelet function that accompany CPB all contribute to the prolongation of the ACT even if heparin levels are inadequate.

Alternatively, individualized heparin and protamine management in children and adults undergoing CPB has been shown to be a more effective method for inhibiting thrombin generation during CPB [53,63,64]. It is associated with improved clinical outcomes, resulting in reduced postoperative bleeding and decreased need for blood transfusions. In some centers, heparin management while on CPB and subsequent protamine administration has deviated from weight-based protocol and ACT measurement to bedside measurements of blood heparin concentration using an automated protamine titration device. Studies have demonstrated that a patient-specific heparin concentration-based protocol to guide administration of heparin for CPB in infants less than 6 months dictates a substantially higher total heparin dose than would have been required by the standard weight-based protocol [54]. Biochemically it appears that this is associated with greater thrombin suppression; however, clinically it might be correlated with more blood product administration [54,60]. Some authors suggest that a modification of the algorithms to make them applicable to neonates might be necessary to avoid excessive blood product administration [53,54,59,60].

Protamine sulfate binds ionically to unfractionated heparin and dissociates it from the heparin–antithrombin complex. Protamine in excess can paradoxically impair coagulation and is a preventable cause of bleeding after cardiac surgery [56,65–67]. This anticoagulant effect can be attributed to its polycationic structure, which inhibits serine proteases resulting in weakened clot strength, clot kinetics, and decreasing platelet sensitivity to adenosine diphosphate receptors and collagen [65–67]. As heparin–protamine mismatch can occur following pediatric CPB considering the large variations in hemodilution related to patient/pump blood volumes and the presence of an immature coagulation system, this might make maintenance of hemostasis challenging, further making necessary the need for individual-based titration of heparin and protamine.

Strategies to reduce bleeding post-bypass include the use of antifibrinolytics and ultrafiltration. Commonly used antifibrinolytics are the lysine analogs tranexamic acid and aminocaproic acid and also aprotinin. The former have been shown to reduce post-cardiac surgery bleeding in both the adult and the pediatric population, although the doses for pediatric cardiac surgery have not been clearly established. Dosing differs between centers, with doses of tranexamic acid commonly ranging between 10 and 15 mg/kg. Aprotinin use is more controversial. It is a serine protease inhibitor that has been shown to decrease bleeding, shorten ICU stay, and reduce mortality in adults. However, studies in adults have shown that its use significantly increased risk of renal failure or stroke. There is thus far no data to support similar findings in children. In pediatric studies, aprotinin reduces significantly the level of anti-inflammatory biomarkers and plasminogen levels [68] and perioperative use of blood products compared with tranexamic acid [69]. Aprotinin administration is accompanied by the risk of anaphylaxis, especially if there has been prior exposure to it.

**Thromboelastography**

Thromboelastography is useful in directing blood product administration post-CPB. It measures whole-blood viscoelastic changes associated with fibrin polymerization. Its ability to generate information about coagulation factor activity and platelet function within a short time has made it an increasingly popular test for monitoring coagulation during and after CPB. This information is translated into a graphical representation. Chapters 7 and 13 present a detailed discussion of anticoagulation and bleeding management.

**Separation from bypass**

Separation from CPB will occur once the child is adequately rewarmed, any air present in the heart or coronary arteries is removed, there is good heart function and there are no arrhythmias or ischaemia. Inotropes will almost always be required. Both epinephrine and dopamine can be used and so can milrinone for its inodilatory properties. In addition, it is important that any important surgical bleeding has been identified and stopped. Blood volume may be necessary immediately after CPB separation and this can be given by the perfusionist via the aortic cannula. Many centers use modified ultrafiltration, which involves ultrafiltration of blood received from the aortic cannula and reinusing it to the right atrium. This process increases the hematocrit, concentrates clotting factors and platelets, increases the blood pressure, reduces the PVR and removes inflammatory mediators. It has been shown to decrease bleeding in children after cardiac surgery significantly. In addition, blood products may need to be administered. It is worth mentioning that neonates are particularly sensitive to disturbances of their ionized calcium levels, following citrated blood infusion. Those with limited cardiac reserve will tolerate this poorly as the myocardium is particularly sensitive to the effects of citrate infusion. It is frequently necessary to administer additional calcium while infusing blood products. In addition, some centers will add nitroglycerine infusion, which theoretically will cause vasodilation in the reimplanted coronary arteries. Although heart block is rare even with VSD closure, atrial pacing wires are often placed, and temporary atrial pacing may be very useful in maintaining heart rate in the desired ranges, i.e. 120–150 for most neonates.

Following CPB separation, echocardiography in conjunction with LAP measurement is used to assess global and regional LV function. Post-CPB myocardial dysfunction may be due to air in the coronaries, inadequate coronary transfer, or poor myocardial protection, or it may simply be a result of a deconditioned LV. LAP is particularly useful for monitoring as it may reflect left
ventricular dysfunction and should remain in situ for the immediate postoperative period. LA overdistension should be avoided because it reflects excessive left ventricular preload. This places the ventricular myofibrils too far to the right on the starling curve, thus reducing contractility. LA overdistension should also be avoided because, after the repair, the PA is anterior to the aorta and close to the origin of the coronaries. Therefore LA distension will cause PA distension, which may compress the coronary arteries. Pulmonary hypertension from any other cause will have a similar effect. Thus the hemodynamic goals of ASO patients following CPB separation would be to achieve adequate cardiac output while maintaining the lowest possible LAP and avoiding pulmonary hypertension. Fluid boluses should be given carefully, and in many patients an LAP of around 6 mmHg with systolic pressure of 55–75 mmHg usually achieves these goals. In practice, fluid should be administered very cautiously as even a small volume of fluid can cause the LAP to rise dramatically. Undesired hypervolemia with high LAP can be corrected rapidly by withdrawing blood, usually 3–5 mL, from the arterial or central catheter.

Chest closure at the end of the operation is occasionally not possible. This may be because of hemodynamic instability or it may be due to a large heart secondary to edema of the myocardium or dilatation. If the chest is left open, it is usually stented and covered with a Silastic dressing. Chest closure should be performed as soon as possible in the postoperative period, preferably within a few days, so as to reduce the risk of infection. Neonates with d-TGA who have undergone an ASO are not usually candidates for early extubation and are therefore transferred to intensive care where stability is achieved over the next few days. An opioid and benzodiazepine infusion is commonly used for sedative purposes. Some centers with aggressive fast-track policies would aim to extubate these babies in the operating room or very early in the postoperative period.

**KEY POINTS: ANESTHETIC MANAGEMENT**

- Induction can be inhalational or intravenous.
- Maintenance with balanced opioid/inhalational technique is often preferred for better hemodynamic control.
- Invasive monitoring (arterial line, central venous pressure) is placed after nasotracheal intubation.
- Nasopharyngeal, rectal, and skin temperatures, neuromonitoring, and TEE or epicardial echocardiography probes are employed.
- Antibiotic prophylaxis is administered before skin incision.
- Corticosteroids and antifibrinolytics are used by most centers.
- Heparin is administered with an ACT goal of > 350 seconds; heparin level measurement systems are often very useful.

- CPB weaning is accomplished after rewarming, intracardiac air is removed, and cardiac function is acceptable, with acceptable rhythm and no signs of ischemia.
- Echocardiography is performed before sternal closure.

**Postoperative management of the ASO**

Patient management postoperatively takes place in the intensive care unit and is tailored to the patients’ preoperative condition and the specific surgery performed. The patient is transferred intubated to intensive care postoperatively, where sedation is continued. The general aims are to achieve hemodynamic stability and carry out careful observation for potential complications.

**Hemodynamic stability and hemostasis**

The adequacy of circulation is assessed both clinically and with interpretation of the data generated from invasive monitoring. Mean arterial pressure should aim to be above 40 mmHg and serum lactate monitoring can be a useful marker of perfusion. LAP monitoring is critical and this should remain between 5 and 8 mmHg. Maintenance intravenous fluids are limited to 50% of normal in the first postoperative day. Fluid challenges should be cautious, as the unprepared LV can be forced onto the downward slope of the Starling curve, precipitating hemodynamic deterioration. In general there is little benefit in terms of blood pressure of volume loading beyond a mean LAP above 10 mmHg. Inotropes such as milrinone and epinephrine are usually titrated for optimization of cardiac contractility and to achieve an adequate perfusion pressure. Immediate and specific postoperative problems include bleeding, left ventricular dysfunction, pulmonary hypertension, and arrhythmias.

There are various factors that predispose to bleeding, including the small size of the patient, the underlying pathophysiology, long CPB time, and extensive dissection with multiple suture lines. Blood product transfusion and coagulation management intraoperatively minimize postoperative coagulopathy. Despite this, additional products may be required in the immediate postoperative period and chest drain output is closely monitored.

Left ventricular dysfunction is common to some degree in the immediate 12 hours postoperatively. It may be a non-specific post-CPB low cardiac output state, dysfunction secondary to a poorly trained LV, or a sign of coronary artery insufficiency. A low cardiac output state – persistent systemic hypotension, increasing LAP, and poor peripheral perfusion postoperatively – should prompt a review of the coronary flow. A 12-lead ECG might identify ischemia, and echocardiography can identify abnormalities of coronary blood flow and assess abnormal regional wall movement. It is worth noting that the neonatal LV is poorly compliant postoperatively, particularly after the ASO, and acute increases of preload.
associated with rapid fluid administration can worsen LV function. For this reason, fluid boluses should be given slowly in small aliquots of 5–10 mL/kg. In addition, the fluid should be given slowly, with careful observation of LAP and the speed and volume of fluid titrated to the LAP.

Ventricular arrhythmias are uncommon in neonates and, if they occur or arrhythmias persist, a coronary artery problem needs to be ruled out. Obstruction to translocated coronary arteries is rare, but the signs include global myocardial dysfunction and an ischemic ECG. Patients with certain types of coronary anatomy, such as intramural coronary arteries or a single coronary artery, are more at risk of postoperative myocardial ischemia because the coronary transfer is technically more demanding [70–72].

Sedation
Postoperative sedation following open heart surgery can be challenging as these patients often have labile cardiovascular function and may require several days of sedation as part of their intensive care management. It is important to try and achieve the optimum level of sedation, which is a balance between hemodynamic compromise and inadequate sedation. An infant struggling against the ventilator risks cardiorespiratory instability, accidental extubation, and loss of lines or drains. Commonly used sedative agents include opioids such as fentanyl, morphine, benzodiazepines such as midazolam, or α agonists such as clonidine. Dexmedetomidine is another α agonist that is used in many units for sedation following open heart surgery, which we will focus on in a little more detail in this section as it appears to have a favorable profile for this specific patient population.

Dexmedetomidine is a selective α2 agonist that has sedative, anxiolytic, and analgesic properties. It has a similar structure to clonidine but with a α2:α1 specificity of nearly 1600: 1 [73–75]. It also has a shorter half-life of 2–3 hours compared with clonidine, which is 12–24 hours [75]. This allows titration by continuous infusion and it has gained increasing popularity for sedation in intensive care units due to its limited effects on respiratory function. Studies have not shown any clinical significant respiratory depression or changes in arterial blood gases [73,76–78]. It has been used successfully both as a bridge to extubation and for sedation of non-intubated patients [76]. Studies have shown that it is efficient and safe for prolonged administration > 96 hours in critically ill children with heart disease. It also significantly reduces the doses of concomitant opioid and benzodiazepine administration [79]. It provides adequate sedation as a first-line single agent while reducing supplemental sedative and analgesic agents. Within doses of 0.25–0.75 μg/kg/hour, the extubation success rate is very high, 94% in a study by Su et al., which supports the concept of fast-track postoperative care [79]. It seems to have no adverse cardiovascular or gastrointestinal effects and reduces ionotropic agent dosing in children with low cardiac output [80,81]. There is a dose-dependent reduction of heart rate that is evident with dexmedetomidine administration, but it does not appear to be a problem clinically [79]. There are authors who suggest its cautious use in patient at risk of bradyarrhythmias and in patients who are receiving medication with a negative chronotropic effect [82–84]. It should be noted that dexmedetomidine is almost completely metabolized by the liver and that its clearance is significantly reduced in the first 3-4 weeks of life; therefore, both loading and infusion doses should be reduced in the neonate accordingly.

Respiratory support
The child remains sedated and ventilated initially after surgery and then sedation and respiratory support are gradually weaned as tolerated. Exubation can occur when the following have been achieved:

- Hemodynamic stability – this includes an adequate blood pressure, a normal heart rate and normal LAP without excessive inotropic support
- Ventilatory requirements are minimal with low inflation pressures and low oxygen requirements
- Adequate urine output and fluid balance has been achieved – a good urine output is usually a positive indicator and is essential to remove excessive fluid from the myocardium, lungs and other organs
- Chest radiograph confirms no excessive fluid, no effusions and no pneumothorax
- Blood gases are normal
- No signs of sepsis

Mediastinal drains
Surgical drains are closely monitored in terms of output as this is often indicative of the adequacy of hemostasis and might necessitate blood product administration. In the majority of cases, the output will decrease in the first few postoperative hours. High drain output associated with hemodynamic changes might require surgical re-exploration because of cardiac tamponade in the very small pericardial space of the neonate. Drains are removed when the output is minimal, commonly in the first 3 days. Removal is followed by a chest radiograph to confirm absence of a fluid collection, lung collapse or pneumothorax. Left atrial lines are removed when no longer required for monitoring, usually before chest drain removal.

Peritoneal dialysis
In many centers a peritoneal catheter is routinely placed at the time of operation in these children and is initially used as a continuous drain to collect the abdominal fluid that commonly collects following CPB in newborns. It might be used to institute temporary peritoneal dialysis postoperatively, although this is not common. The indications for starting peritoneal dialysis are oliguria or anuria unresponsive to fluid and diuretic therapy, fluid overload, or hyperkalaemia.

Sepsis
Antibiotic prophylaxis begins in the preoperative period, with the first dose being given at induction. In our center
a further three postoperative doses of antibiotics are given prior to them being discontinued. This policy is different in situations where the chest has to be left open, where broad-spectrum antimicrobials are continued for a total of 5 days, or during the duration of the chest being open.

**Long-term complications and outcomes of the ASO**

Generally low operative mortality and excellent childhood survival have been described by several groups [85–87]. Between 2005 and 2009 the operative mortality of 1,671 ASOs in the Society of Thoracic Surgeons Congenital Heart Surgery Database was 2.2% for TGA/IVS and 5.5% for TGA with VSD. Postoperative survival at 15 years is thought to be > 85% in many units worldwide. Given these excellent long-term survival rates, the emphasis for outcomes analysis in ASO patients is shifting from mortality to reducing morbidity and improving quality of life.

**Late complications**

There are predictable but treatable long-term problems associated with the ASO, the main ones being PA and right ventricular outflow tract (RVOT) stenosis, neo-aortic valve insufficiency, and coronary artery obstruction.

**PA/RVOT stenosis**

Right ventricular outflow stenosis tract tends to be the result of supravalvular pulmonary stenosis and is the most common mid- to long-term complication after ASO, occurring in 2–17% of cases [88–91]. TGA with VSD and prior neopulmonary artery reconstruction with a polytetrafluoroethylene patch have been correlated with an increased risk of reintervention on the RVOT [90]. Surgical correction requiring reoperation is rare, with the majority of cases being treated by percutaneous balloon dilatation in the interventional catheterization laboratory [88–91]. Therefore it is not expected to be a long-term concern with regard to the morbidity of these patients.

**Neo-aortic valve**

After the ASO, the structurally formed pulmonary valve becomes the neo-aortic valve. Early on in the ASO era, concerns were raised about the durability and longevity of the neo-aortic valve [92–94]. In follow-up studies it has been demonstrated that the incidence of moderate and severe aortic regurgitation is low at 20-year follow-up, with 85–98% of the patients expected to have trivial or mild regurgitation. Risk factors for neo-aortic regurgitation include prior PAB, aortic root dilatation, discrepancy of the great arteries, and complex TGA associated with VSD, TBF, and arch obstruction [88,89,95–97]. The reoperation rate for aortic valve repair is very low, reported at 0.3–5% [88–91,96–99]. The development of neo-aortic insufficiency after ASO may be attributable to the presence of a morphological PV in the systemic circulation, although the incidence of clinically significant neo-aortic insufficiency in the general ASO population remains low. LVOTO is a risk factor for development of significant regurgitation.

**Coronary artery obstruction**

The true incidence of late coronary artery stenosis following ASO is unknown, as patients may be asymptomatic (because of the denervation of the heart during the ASO), with standard electrocardiogram or echocardiography usually showing no sign of ischemia. The reported incidence of stenosis/occlusion lies in the range of 2–9% [92,97,100,101] and risk factors are thought to be single coronary artery [100] and complex coronary anatomy [90,102]. Furthermore, the oldest survivors of ASO are only just approaching adulthood and there is limited data collected regarding how the natural atherosclerotic process affects these patients and whether the neonatal surgical trauma adds to the risk in the long term.

**Myocardial function**

Abnormal myocardial perfusion scans at rest and at peak have been demonstrated in healthy and otherwise asymptomatic individuals long after the ASO [92], associated with diminished exercise capacity [85,103]. It is thought that variant coronary patterns and a VSD are associated with chronotropic impairment of the heart [104]. An echocardiography study of asymptomatic children following ASO with patent coronary arteries found lower fraction shortening and ejection fraction [105]. In addition, dobutamine stress testing unmasked wall motion abnormalities in three-quarters of the patients, corresponding to reversible myocardial perfusion defects [105]. It is unclear what the clinical relevance and therapeutic consequences of these findings are.

**Quality of life and neurodevelopmental issues**

Reports on the perceived quality of life have yielded varying results depending on the age [106,107]. Self-reported quality of life and the degree of social independence seem excellent in the majority of young adults, but the same has not been found in younger patients [108]. Neurodevelopmental assessment of teenagers 15 years after the ASO shows satisfactory average scores, although they are consistently below expected levels, independent of the bypass strategy chosen at the time [109]. One-third required additional tutoring, a quarter had received special education or psychotherapy, and one in six had repeated a grade level at school [92,109]. Chapter 11 presents more detailed information about longer-term neurodevelopmental outcomes.

**LVOTO outcomes**

The feasibility of ASO in some patients with TGA/LVOTO has been demonstrated with good outcomes in recent years [6,24,25,110]. There is a 5% risk of recurrent LVOTO and a 7% risk of LVOTO reoperation. This is an improvement on the reported incidence of a 25% risk of LVOTO reoperation after the Rastelli procedure at a follow-up of
5–10 years [6]. The incidence of aortic regurgitation after ASO for TGA/LVOTO is higher (13%) compared with ASO repair for simple TGA (4%) [97,111]. An advantage of the ASO-type repair over the Rastelli seems to be the lack of need for an RVOT conduit and for conduit reintervention.

**TBH long-term outcomes**

Despite the palliative nature of the correction of the TBH, the functional outcomes are encouraging. Single-stage TBH repair has shown excellent early and mid-term outcomes [112–117]. The complexity of corrective surgery is determined by morphological features and by associated lesions; however, associated cardiac anomalies or unusual coronary pattern are not thought to be risk factors for early or late mortality [116]. However, complex anatomy continues to be a risk factor for long-term morbidity in this subset of patients. Early mortality seems to be low, at approximately 2%, with an 85% survival rate at 15 years [115–117]. The majority of patients have normal biventricular function and do not require any cardiac medications. Long-term complications have been identified as aortic valve regurgitation and dilatation of the neo-aortic root. The incidence of moderate or above moderate aortic regurgitation is reported to be < 10%, with no need of aortic valve repair or replacement in the first decade of life; however, some studies [113–117] show increased risk of progressive aortic valve regurgitation in the second decade of life. In general, neurological outcome is good, with only 10% showing some neurological impairment [112].

**Rastelli procedure outcomes**

The Rastelli procedure has low early and late mortality rates. The need for reintervention increases with time and is usually for stenting of conduit stenosis or a replacement of the RV to PA conduit to relieve RVOTO. The need for these subsequent procedures occurs in most patients regardless of the technique used for repair; however, these can be performed with low morbidity and mortality. Although arrhythmias are a common immediate postoperative problem, pacemaker insertion is usually not required in the majority of patients.

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**KEY POINTS: POSTOPERATIVE MANAGEMENT**

- Postoperative patient management takes place in the intensive care unit.
- Invasive monitoring is maintained until extubation.
- Timing of extubation depends on the hemodynamic condition.
- Persistent low cardiac output syndrome or arrhythmias may herald a coronary artery problem.

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**Congenitally corrected TGA**

**Anatomy**

Congenitally corrected transposition of the great arteries, also known as levo-TGA (ccTGA or L-TGA), is a rare complex congenital cardiac defect with an unfavorable natural history. It is defined by AV discordance as well as VA discordance. A right-sided RA connects via a right-sided mitral valve and a morphological LV to a right-sided PA. The left-sided LA connects via a left-sided tricuspid valve and RV to the aorta. Some centers also refer to this lesion as the “ventricular inversion” form of TGA, because this is in essence the main anatomical abnormality in l-TGA (Figure 24.13).

This lesion arises during the point of embryological development when the primitive heart tube folds toward the left. The proximal part, which is the origin of the LV, becomes displaced to the right, and the distal portion, which develops as the RV, develops on the left. The connection of the folded tube to the conotruncus is variable but usually there is continuity of the aorta with the left side and the developing RV.

This AV and VA discordance in isolation creates neither severe physiological derangement nor cyanosis. The two main problems relate to the systemic position of the RV and tricuspid valve as well as to the fact that there is a high incidence of associated cardiac anomalies in ccTGA, which occur in up to 98% of the patients, with a broad spectrum of severity.

Anatomic features in addition to AV and VA discordance that complicate ccTGA include [118]:

- Perimembranous or malaligned VSD (50–80%)
- Multiple or remote VSDs
- Multi-level LVOTO (50%) secondary to pulmonary atresia, or subpulmonary stenosis
- TV anomalies (25–90%)
- Straddling or overriding AV valves
- Abnormalities and disturbances of the AV conduction system
- Ventricular hypoplasia
- Coronary anomalies
- Dextrocardia with or without situs abnormalities.

Approximately 70% of patients will have a VSD and approximately half will have LVOTO, whereas pulmonary stenosis in isolation is rare. Systemic valve (tricuspid) abnormalities are intrinsic to ccTGA, although only half of the patients will have functional consequences as a result. The valve resembles Ebstein’s malformation without completely reproducing it, with the posterior and septal leaflets being tethered to the posterior RV wall. This abnormality tends to limit the long-term functional reliability of the tricuspid valve in the systemic circulation.

The AV node position is also abnormal and is located between the orifice of the RA appendage and the mitral valve annulus, as opposed to being in the apex of the triangle of Koch. Disturbances of the AV conduction system are common and thought to be secondary to fibrosis of
the junction between the AV node and the AV conduction system.

**Coronary anatomy in ccTGA**
The coronary artery anatomy in ccTGA is inverted with the right sided coronary artery giving rise to the Left Anterior Descending (LAD) and circumflex arteries and the left sided coronary becoming the right coronary artery.

**KEY POINTS: ASSOCIATED ANOMALIES IN CCTGA**
- The anomalies associated with ccTGA can be summarized as follows:
  - Dextrocardia (25%) with/without situs inversus
  - Multi-level LVOTO (50%)
  - Perimembranous or malaligned VSD (50–80%)
  - Multiple or remote VSDs
  - Tricuspid valve abnormalities (25–90%)
  - Straddling AV valves
  - Ventricular hypoplasia
  - Coronary anomalies
  - Interruption or abnormally situated conduction pathway.

**Pathophysiology and natural history**
In ccTGA, the TGA is physiologically corrected, giving rise to a normal *series* circulation where deoxygenated blood is oxygenated in the lungs prior to entering the systemic circulation. The morphological LV is the pulmonary ventricle and empties deoxygenated blood into the PA; the LA receives oxygenated blood from the PV, which enters the aorta via the morphological RV. The RV and tricuspid valve are not designed for long-term function in a high-pressure circuit. In terms of the associated cardiac lesions, the physiology of patients with a VSD and/or LVOTO is identical to those who have normal segmental anatomy with the aforementioned cardiac lesions.

Although it is a highly variable lesion, ccTGA is known to have a generally unfavorable natural history. Unoperated patients have a 32% prevalence of CHF and a 25% mortality probability by the fourth decade of life.

The age of presentation and natural history of patients with ccTGA depend on the combination and severity of associated cardiac defects. It is rare to have patients without any significant associated lesions, and those who do are likely to survive into adulthood with generally normal functional status. They might present with symptoms of tricuspid (systemic) valve regurgitation, impaired systemic ventricular function and rhythm disturbances at approximately the fifth decade of life [119].

Patients with associated defects present with a spectrum of symptoms that range from cyanosis to CHF. ccTGA patients can be thought of in two clinical subsets in terms of anatomy: those who have IVS and those with a VSD. The latter can be further subdivided into three groups according to the presence and degree of left ventricular outflow obstruction: those with minimal PA stenosis, those with pulmonary atresia or severe pulmonary stenosis and those with pulmonary obstructive venous disease.

Cyanosis therefore will be present in patients who have a VSD and severe or complete LVOTO, where the pulmonary blood flow is decreased. In patients with a VSD and little or no LVOTO, systemic right ventricular failure, and thus CHF, will be the main symptom. These patients
are similar to those with normal segmental anatomy and VSD with pulmonary blood flow obstruction. The main difference is the fact that the systemic valve is the tricuspid valve, which can lead to valvular insufficiency secondary to exposure to systemic pressures. This further exacerbates the volume overload on the systemic and morphologic RV, which, in the presence of a VSD and high Qp/Qs, is already overloaded.

**Diagnostic features**

As with TGA, ccTGA may be present within a spectrum of cyanosis or CHF as previously mentioned. Two-dimensional echocardiography reliably diagnoses ccTGA and the presence of associated anomalies. Cardiac MRI is now used commonly to further evaluate these complex lesions and is able to provide detailed information about anatomy, function and flow. Cardiac catheterization is not routinely performed and is reserved for assessment of those patients who have pulmonary vascular occlusive disease and is frequently done in conjunction with cardiac MRI to give detailed information about PVR. Many centers including ours now have combined catheter laboratory and MRI suites in which patients can undergo both MRI and cardiac catheterization.

**Surgical options**

Surgical treatment has been available for over 50 years, but optimal surgical management of ccTGA seems to be controversial, due to its variability and complexity. The first surgical repairs for ccTGA were performed by Anderson and Lillehei in 1957. Initial procedures for ccTGA did not correct AV discordance, leaving the RV in a systemic position and the LV in the pulmonary circuit, a strategy that has come to be known as “physiologic repair” [118,119]. In the past two decades, anatomic repair has been considered a better option. Although in the mind of most surgeons the anatomic repair is probably a more attractive option in principle, it is debatable which is the best surgical approach for ccTGA. Given that ccTGA is a relatively rare lesion and most surgeons will not have the opportunity to operate on large numbers of patients, the learning curve for such complex operations is an important consideration. The specific techniques employed will depend to a large extent on the anatomic features, which are highly variable, but also on the team experience and philosophy.

There are various surgical options available for various anatomic situations involving ccTGA. These can be classified into three categories according to which ventricle is the post-repair systemic ventricle:

- **Systemic left ventricle**
  - Classical (physiologic) repair
  - Isolated tricuspid valve repair/replacement
  - Multisite pacing
- **Systemic left and right ventricle**
  - Senning–ASO (double switch procedure)
  - Senning –Rastelli
- **Systemic left and right ventricle**
  - Fontan operation

**Physiologic repair**

Traditional repair in ccTGA patients consists of repair of the associated cardiac defects while maintaining the congenital anatomy. It therefore addresses VSD closure, relief of LVOTO, conduit insertion, and valvular repair or replacement. The unfavorable outcome for physiologic repair has been well documented [122] and the significant early and late morbidity and mortality have been the main reasons for adopting anatomic repairs, despite their more complex nature.

The main complications with physiologic repair to some extent relate to the natural history of the lesion. The physiologic repair creates a situation similar to that of ccTGA with IVS (without LVOTO). The main postoperative problems are systemic valve regurgitation, which occurs even in the absence of surgical manipulation [119], right ventricular dysfunction in approximately half the patients, and also complete heart block requiring pacemaker insertion in up to a quarter of patients. A major factor in the unfavorable postoperative natural history is the Ebstein-like TV, which tends to limit the long-term functional reliability of the valve in the highly pressurized systemic circulation.

However, despite these limitations, the physiologic operative approach may still be useful in highly selected cases. Patients with good right ventricular function, good tricuspid valve function, balanced ventricles, and favorable septation anatomy may be suitable candidates, especially if a relative contraindication to anatomic repair exists, such as poor mitral valve function, coronary anomalies, small atrium, dextrocardia, or inlet VSD features, which may complicate anatomic repairs [118].

**Anatomic repair**

Anatomic repair is a generic term for either an ASO and Senning procedure (double switch) or a Senning–Mustard
and Rastelli operation. The aim of these procedures is to create VA and AV concordance. The former was first performed in the late 1980s by Imai, Yagihara, Mee, and others [118,122,123]. A decade later, Ibiwi described an atrial repair in combination with the Rastelli operation for cases of ccTGA with LVOTO, and since then, anatomic repairs of both varieties have a prominent place in the management of ccTGA. They are the preferred approach in patients with good mitral valve function, balanced ventricles and a septatable heart. Patients with poor RV or TV function would also be candidates for this type of repair as physiologic repair in these patients almost always have an unfavorable outcome.

**Double switch procedure**
The aim of the procedure is to create VA and AV concordance in what is a combination of the ASO and Senning procedures. It can be simplified as a three-step procedure. First, the VSD is closed. The great arteries are switched to their respective ventricles, therefore creating VA concordance. The mitral valve and the morphological left ventricle become the systemic AV valve and ventricle, and the tricuspid valve and morphological RV become the pulmonary AV valve and ventricle. Lastly the Mustard or Senning part of the operation creates an intracardiac baffle which redirects blood from the RA to the morphological RV via the tricuspid valve, which is oxygenated via PA delivery to the lungs. Similarly the oxygenated blood from the LA is redirected to the LV. This creates AV concordance (Figures 24.14 and 24.15) This procedure is indicated in patients with deteriorating systemic ventricle dysfunction, in the presence of systemic (tricuspid) valve regurgitation. Good LV function and no outflow obstruction is a prerequisite for this type of surgical repair.

If the patient has an IVS, or has had a previous physiologic repair, the anatomic LV will often have undergone involution, and a PAB is placed to “train” the LV, with periodic assessment by echocardiography, catheterization, or MRI to determine whether adequate training has occurred. At times, tightening of the existing PA band is needed before the double switch is attempted.

**Senning and Rastelli**
The combination of the Senning and Rastelli procedures has been undertaken in patients with ccTGA that have a VSD and RVOTO, where a valved conduit is placed between the RV to PA.

**Fontan procedure for ccTGA**
The Fontan operation commits both RV and LV to the systemic circuit, and patients having this approach are unsuitable for a biventricular repair strategy based on anatomic considerations. The most accepted subset of patients where the Fontan has been used are those with large VSDs that are unsuitable or at high risk for ventricular septation with complex LVOTO. Data regarding the outcome of Fontan vs. other repairs in patients with ccTGA remain limited.

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**KEY POINTS: SURGICAL OPTIONS**
- RV systemic ventricle after surgery
  - Classical (physiologic) repair
  - Isolated tricuspid valve repair/replacement
- LV systemic ventricle after surgery
  - Senning and ASO (double switch procedure)
  - Senning and Rastelli
- Systemic LV and RV
  - Fontan operation

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**Anesthetic considerations and perioperative management**

**Preoperative assessment**
The main perioperative risks in patients with ccTGA are tricuspid valve regurgitation, RV dysfunction, congestive cardiac failure and rhythm abnormalities, mainly in the AV conduction system, and heart block. The pre-anesthetic visit should focus on identifying and risk-stratifying the presence of these, by carefully assessing the patient in terms of history, examination, review of the clinical notes, laboratory results and review of echocardiography, cardiac MRI and cardiac catheterization. A detailed understanding of what the cardiac defects are, the presence and degree of LVOTO, and the presence of pulmonary vascular occlusive disease and its response to pulmonary vasodilators is vital. History and examination should focus on elucidating
Double switch operation: Senning operation with the arterial switch procedure. Ao, aorta; PA, pulmonary artery; PV, pulmonary veins; SVC, superior vena cava; IVC, inferior vena cava; LV, left ventricle; RV, right ventricle.

Figure 24.15

Induction and maintenance of anesthesia follow the principles highlighted in the section on pathophysiology of ccTGA above. These children may be compromised with little cardiac reserve, so induction has to be tailored to the specific child and the situation. Invasive intraoperative monitoring (arterial line, central venous pressure, and TEE) is necessary, as well as systemic AV valve competency. Ventricular mass of the morphological LV is particularly important mainly to check that the LV mass is adequate to become the systemic ventricle. Occasionally a PAB is placed for that purpose and its outcome has to be reviewed.

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The intermediate outcome data for patients undergoing the double switch procedures are encouraging, with some studies showing 100% survival at 36 months follow-up [125]. Gaies et al. from Ann Arbor, Michigan analyzed the long-term outcome for the Senning and ASO as well as Senning–Rastelli operations. Survival of the double switch procedure was found to be 91% at 10 years compared with 55% at 5 and 10 years of the Senning and Rastelli operation [126]. By contrast, Brawn et al. did not find a significant difference in 10-year survival between the two groups, which was below 85% [127]. He did find, though, that patients who required preliminary LV retraining did significantly worse in terms of freedom from LV dysfunction.

The long-term risks and benefits are not yet completely characterized, and although it seems that anatomic repairs have a favorable impact on the natural history of ccTGA, more data and long-term outcomes need to be collected and a universally reliable strategy continues to elude us.

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A full reference list for this chapter is available at: https://www.wiley.com/go/andropoulos/congenitalheart


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Anesthesia for the Patient with a Single Ventricle

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Introduction

In the early 1970s, Fontan and Baudet [1] and Kreutzer et al. [2] independently introduced operative treatment of tricuspid atresia (TA) that resulted in nearly normal systemic arterial oxygen saturation and normal volume work for the single functional systemic ventricle. This procedure, subsequently referred to as the Fontan operation, created a series circulation that requires the single ventricle to pump fully saturated blood only to the systemic circulation, thereby reducing the pressure and volume work to that of a normal systemic ventricle. The systemic venous drainage passes directly through the pulmonary vascular bed without benefit of a pumping chamber. The child’s pulmonary vascular resistance (PVR) must be low to maintain the pulmonary circulation and the cardiac output (CO) on which it depends. Since that time, the principle of the Fontan operation has been applied to the full spectrum of cardiac lesions with one functional ventricle. Suitable physiology for ultimate repair by a modification of the Fontan procedure is predicated on carefully planned and appropriately timed and executed palliative operations designed for the specific patient’s single-ventricle physiology. Essentially all patients with a single functional ventricle now undergo staged palliation, resulting in completion of the Fontan circuit at 18 months to 3 years of age. The majority undergo a neonatal palliative procedure, followed by a superior cavopulmonary connection (bidirectional Glenn procedure) at 3–6 months of age in all patients. This chapter will present these principles first by using hypoplastic left heart syndrome (HLHS) as the most common single-ventricle congenital cardiac lesion. Tricuspid atresia will then be presented, as the most common hypoplastic right heart lesion. Finally, other forms of single-ventricle lesions will be discussed.
Hypoplastic left heart syndrome

Incidence, anatomy, and natural history

Hypoplastic left heart syndrome represents the fourth most common defect presenting in the neonatal period and accounts for 7.5% of the newborns presenting for treatment of congenital heart disease (CHD) sufficiently affected to require early therapeutic intervention. The overall incidence of HLHS is 1.4–3.8% of all CHD, but it accounts for 23% of deaths from CHD within the first week of life, and 15% of CHD deaths within the first month [3]. Recent work by Hinton et al. demonstrated a high heritability component to HLHS, suggesting HLHS as a severe form of valve malformation with inheritance as a complex trait, and emphasizing the importance of screening first-degree relatives of HLHS patients [4].

Hypoplastic left heart syndrome is characterized by a single right ventricle (RV) and hypoplasia of the left side of the heart to varying degrees, involving either severe aortic stenosis (AS) or aortic atresia (AA), and severe mitral stenosis or mitral atresia (MA), and a very hypoplastic left ventricle (LV) (Figure 25.1) [5]. Blood returns from the pulmonary veins to the left atrium (LA), but because of obstruction to mitral and aortic flow, blood flows left to right across the atrial septum, to the enlarged and dilated right atrium (RA) and RV, which must support the outputs of both the systemic and pulmonary circulations. Blood flows from the pulmonary artery (PA) right to left through the patent ductus arteriosus (PDA) to the aorta, supplying the systemic arterial circulation. Blood must flow retrograde to perfuse the brachiocephalic vessels, aortic root, and coronary arteries. In cases of severe AS there may be some degree of antegrade aortic valve flow, but the hallmark of HLHS is retrograde flow in the ascending aorta supplying the majority of the blood flow. Variations of hypoplasia of the left heart involving larger LV, mitral valve and aortic valve sizes are often amenable to two-ventricle surgical repairs, and are presented in detail in Chapter 22.

Without intervention, HLHS is uniformly fatal in the first several months of life, as the PDA narrows and closes, resulting in diminished blood flow to the systemic circulation and coronary arteries, and an ensuing state of circulatory shock heralded by poor perfusion, lactic acidosis, and respiratory failure.

Pathophysiology of HLHS

Hypoplastic left heart syndrome results in a parallel circulation, where pulmonary and systemic venous blood mix in the RV, which is in direct communication with the pulmonary circulation (through the PA), and the systemic circulation (through the PDA). The PDA must be maintained after birth with infusion of prostaglandin E1 (PGE1). There is a delicate balance between pulmonary (Qp) and systemic (Qs) blood flow, with Qp:Qs near 1:1 as the optimal state to maintain adequate perfusion of lungs and body. As PVR decreases in the hours and days after birth, Qp:Qs increases, and may reach 2:1 or 3:1. The resultant pulmonary overcirculation can result in pulmonary interstitial and alveolar edema, tachypnea, and retractions, and can culminate in respiratory failure requiring assisted ventilation. Increasing the FiO2 or hyperventilating the patient will further lower PVR, and exacerbate pulmonary edema. An even more important effect of increasing Qp:Qs is the “steal” effect, diverting flow away from the systemic circulation and compromising blood flow to both the body and the coronary arteries, resulting in cardiogenic shock with poor perfusion and lactic acidosis. Maneuvers to increase PVR by maintaining FiO2 at 0.21, and allowing PaCO2 to increase, either via spontaneous respiration or, if mechanically ventilated, decreasing minute ventilation, are important treatment strategies. The former practice
of delivering subambient FiO₂ via mechanical ventilation will decrease both systemic and cerebral oxygenation significantly and has been abandoned in favor of maintaining spontaneous respirations preoperatively, and intervening surgically in the first few days of life [6]. If the PDA narrows, Qp:Qs can increase, but in this scenario systemic perfusion will also be compromised and cardiogenic shock ensues. The optimized preoperative state for HLHS in the neonatal period is usually a spontaneously breathing neonate, “self-regulating” their Qp:Qs with slightly elevated PaCO₂ due to tachypnea. Diuretics (i.e., furosemide) are very useful preoperatively to limit blood volume recirculating through the lungs. Nasal continuous positive airway pressure (CPAP) may be helpful to provide positive pressure to relieve respiratory distress and elevate the PVR while maintaining spontaneous respiration. Tracheal intubation and mechanical ventilation are reserved for the most severe respiratory insufficiency or those who have anatomic variants (e.g. restrictive intra-atrial communication) that markedly diminish pulmonary blood flow (PBF). Steal of flow from the systemic circulation may also result in mesenteric ischemia, and necrotizing enterocolitis may occur in preoperative HLHS patients. Early surgery, before severe derangements in Qp:Qs ensue, is important in preventing complications.

Anatomic variables can have a major impact upon the observed physiology. Some restriction to pulmonary venous return, such as occurs with left-to-right flow across the foramen ovale, is desirable as it tends to balance pulmonary and systemic resistance, and thus Qp:Qs. Infants who lack that restriction, such as those with an ASD or unrestricted anomalous pulmonary venous return, tend to exhibit high Qp:Qs. In contrast, infants presenting with an intact atrial septum and no alternative decompressing vein have severely obstructed pulmonary venous return, and consequently have an extremely low Qp:Qs. Despite therapeutic maneuvers designed to lower PVR and promote PBF, these infants exhibit marked hypoxemia and require urgent intervention to decompress pulmonary venous return in order to have any hope of survival. A number of other factors, such as atrioventricular (AV) valve regurgitation, and hemoglobin level, can affect the pathophysiology of HLHS. An overview of single-ventricle pathophysiology is presented in Figure 25.2.

In the current era, the majority of HLHS cases are diagnosed in utero after an abnormal screening ultrasound at 18–22 weeks’ gestation is confirmed by a detailed cardiac examination. In the Single Ventricle Reconstruction Trial, a multicenter study of over 500 HLHS patients sponsored in the US and Canada by the Pediatric Heart Network of the US National Heart, Lung, and Blood Institute, 76% of HLHS patients were diagnosed in utero, with a range of 55–85% across the 14 centers [7]. Fetal catheter intervention may be attempted for some HLHS patients, either to dilate the aortic valve or to dilate and stent a restrictive atrial septum (fetal interventions are discussed in detail in Chapter 15). Although prenatal diagnosis alone has not been demonstrated to improve HLHS survival, late postnatal diagnosis and long distance from a cardiac surgical center affect mortality, with most mortality occurring preoperatively [8]. Therefore, prenatal diagnosis and subsequent delivery in or near a cardiac surgery center may improve mortality. After initial assessment, immediate treatment in the delivery room for known HLHS patients involves institution of PGE₃, placement of umbilical arterial and venous catheters, maintenance of spontaneous ventilation on room air and transfer to a neonatal or cardiac intensive care unit (ICU). A postnatal transthoracic echocardiogram is performed both to confirm the initial diagnosis and to assess other anatomic information, such as presence of AV valve regurgitation or restrictive atrial septum, size of the LV, and presence of anomalous pulmonary venous return, or other less common but important details, such as coronary artery fistulae or sinusoids to the LV. Because 15–30% of HLHS neonates also have extracardiac anomalies or genetic syndromes such as the CHARGE association or chromosomal abnormalities, a thorough evaluation for these problems should also be performed [3]. Late diagnosis occurs when the PDA narrows and the infant demonstrates clinical signs of low CO and shock, prompting echocardiographic assessment. Resuscitation of the infant, including immediate PGE₃ infusion, must be initiated emergently. The magnitude and distribution of acquired vital organ dysfunction usually relate to circulatory instability at the time of diagnosis. Infants who have suffered a profound or protracted shock state at the time of diagnosis can demonstrate a wide spectrum of injury to renal, central nervous system, cardiac, gastrointestinal, or hepatic systems [9–11]. These derangements may necessitate a delay in operative intervention to permit recovery.

Surgical and transcatheter approaches and outcomes

In 1979, Norwood et al. described a palliative operation for HLHS performed in the neonatal period, and later described the staged second operation, a Fontan palliation, which resulted in the first long-term survivors of this palliative approach [12]. The Norwood stage I palliation involves reconstruction of the diminutive ascending aorta, usually with a cryopreserved homograft patch, and creation of an outflow from the systemic RV through the pulmonary valve, which also provides blood flow to the native aortic root and coronary arteries. The pulmonary valve becomes the “neo-aortic valve” [13] (Figure 25.3). In addition, an atrial septectomy is performed to provide unrestricted left-to-right blood flow across the atrial septum. In this process, the main PA is transected, the proximal portion of the PA may be incorporated into the aortic repair and the underside of the PA bifurcation is oversewn. Pulmonary blood flow is provided with a polytetrafluoroethylene (PTFE) shunt, either via the systemic-to-pulmonary route (right innominate or subclavian artery to right PA), or via an RV–PA conduit (Sano shunt; see later). Critical surgical technical issues include
the base of the anastomosis between the pulmonary valve and the aortic valve, as any obstruction can affect the already tenuous coronary blood flow. Another important issue is the removal of any residual ductal tissue in order to prevent residual coarctation. Because of the aortic arch reconstruction, cardiopulmonary bypass (CPB) techniques must provide a bloodless surgical field during this period; either deep hypothermic circulatory arrest (DHCA), or regional cerebral perfusion (RCP) is utilized for this purpose. Preference for one or the other technique is largely surgeon and institution dependent; details of each technique as well as short and longer-term outcomes are discussed in Chapter 7.

**Systemic-to-pulmonary vs. RV-to-pulmonary shunts**

The systemic-to-pulmonary artery shunt (also termed modified Blalock-Taussig shunt [mBTS]) is a 3.0- to 4.0-mm PTFE graft that provides continuous flow into the PA. Resistance to flow is proportional to the length of the shunt, inversely proportional to the fourth power of the radius, and also a function of the pressure drop across the shunt, e.g. influenced by the PVR and systemic vascular resistance (SVR). Kinking or distortion of the shunt or the PA obviously interferes with flow. Because there is continuous “run-off” of flow from the systemic circulation into the PA, these patients remain at risk for steal from the systemic circulation as PVR decreases. This is thought to be the major pathophysiological reason for the frequent instability observed in the early postoperative period in these patients. In 2003, Sano et al. reported improvement in stage I survival in a small number of patients at one institution when PBF was provided by an RV–PA shunt (5–6mm PTFE graft) rather than via an mBTS shunt [14] (Figure 25.4). The physiologic reason for this was felt to be due to the higher diastolic blood pressure, because the RV–PA conduit arises proximal to the neo-aortic valve, and thus there is no flow into the PAs during diastole, limiting diastolic run-off and coronary ischemia. The Single Ventricle Reconstruction Trial was
designed to test the hypothesis that stage I survival would improve with utilization of the RV–PA shunt, with an endpoint of death or transplantation in the first 12 months [5]. In all, 555 infants were randomized in 2005–2010 to either mBT or RV–PA shunt. About 10% of subjects were assigned a shunt type, but were required to cross over to the other shunt type because of anatomic considerations. At 12 months, 36.4% of the mBT shunt subjects died or were transplanted, compared with 26.3% for the RV–PA shunt ($P = 0.010$). However, overall complication rates in the RV–PA shunt group were higher (72 vs. 46 per 100 infants, $P = 0.03$); and the number of infants experiencing one or more complications was also greater with the RV–PA shunt (39 vs. 28%, $P = 0.03$). After 12 months, the hazard ratio for death or transplantation was not different between the two types of shunts. In contemporary practice the shunt type used depends largely on surgeon and institutional preference.

In a later publication specifically examining the rate and causes of 30-day in-hospital mortality in the Single
Ventricle Reconstruction Trial subjects, 16% of subjects died during the initial hospitalization; 12% in the first 30 days after Norwood stage I palliation [15]. Shunt type was not a significant risk factor for mortality after multivariable analysis, but the mBTS was an independent risk factor for cardiopulmonary resuscitation. Independent risk factors for both 30-day and total in-hospital mortality included low birth weight, genetic abnormality, extracorporeal membrane oxygenation (ECMO) after the procedure, and open sternum; longer duration of DHCA was an independent risk factor for hospital mortality. Independent risk factors for major morbidity (renal failure, sepsis, increased duration of ventilation and hospital stay) included genetic abnormality, lower center/surgeon volume, open sternum, and additional post-Norwood operations.

Inter-stage mortality occurring after the initial hospitalization, but prior to the bi-directional cavopulmonary connection usually performed at 3–6 months of age, has been a persistent problem after stage I palliation for HLHS. The physiology of the HLHS patient remains tenuous after the initial palliation, as the parallel circulation, with all systemic and pulmonary output passing through the single systemic ventricle, is not changed by the operation. The coronary circulation remains at risk and the Qp:Qs balance is still labile. Significant hemodynamic perturbations may be caused by dehydration from viral gastroenteritis, upper respiratory infections, or micro-aspiration episodes caused by recurrent laryngeal nerve injury that frequently accompanies stage I palliation. In the Single Ventricle Reconstruction Trial, of 426 subjects discharged from the hospital, 50 died interstage (12%) [16]. The interstage death rate was greater for the mBTS patients (18%) than for the RV–PA shunt patients (6%, \( P < 0.001 \)). Risk factors for interstage death included gestational age <37 weeks, Hispanic ethnicity, AA/MA, greater number of post-Norwood complications, census block poverty level, and moderate to severe AV valve regurgitation.

With a combined 28% mortality in the Single Ventricle Reconstruction Trial after the Norwood stage I palliation and prior to bi-directional cavopulmonary anastomosis, the challenges of caring for this group of patients are evident. Death after the cavopulmonary connection in the first year of life is less common; the stabilizing effect on the pathophysiology of HLHS (see later) is the most significant factor.

**Hybrid procedure**

Despite continuing improvements in the perioperative management of infants with HLHS, as noted earlier, certain populations of patients remain at higher risk and demonstrate a more significant level of morbidity and mortality during and after surgical stage I palliation [17]. In general, these risk factors include birth weight <2.5 kg, gestational age <34 weeks, ascending aortic size <2 mm, poor ventricular function, severe tricuspid regurgitation, restrictive atrial septum, and the presence of additional cardiac or non-cardiac anomalies [18,19]. Continuing advancements in interventional cardiology techniques have facilitated the development of alternative therapeutic strategies for these subpopulations of patients; due to the utilization of both surgical and interventional catheterization procedures, these interventions are known as “hybrid” procedures. The hybrid procedure is performed in the catheterization laboratory, operating room (OR), or “hybrid” proceduresuite. It consists of median sternotomy without CPB, surgical placement of bilateral PA bands, and placement of a stent in the PDA, which is performed by the interventional cardiologist with access obtained in the main PA (Figure 25.5) [20]. The atrial septum can be stented if restrictive. Advantages of hybrid procedures include the avoidance of CPB and/or DHCA in the neonatal period, as well as the provision of an extended waiting period for infants who require cardiac transplantation or who may be eligible for biventricular repair. The hybrid procedure is further detailed in Chapter 29.

Modifications to the hybrid procedure continue to occur as newer devices become available, such as internal self-expanding flow restrictors, which can be utilized in...
and Cheatham recently reported an overall survival of 82.5% in a cohort of 62 patients without known high-risk characteristics, with 15 patients having completed the Fontan procedure [26]. With continuing experience and technical modifications, the hybrid procedure may allow an increased survival opportunity for high-risk patients and those awaiting cardiac transplantation or the potential for biventricular repair. Honjo et al. reported early and mid-term outcomes of 58 patients undergoing Norwood with mBTS \( (n = 39) \), compared with hybrid \( (n = 19) \) performed from 2004 to 2007 at the Hospital for Sick Children, Toronto [27]. The review was retrospective, and the treatment strategy not randomized, but they did exclude patients receiving the hybrid strategy for salvage of very sick patients, or pre-cardiac transplant \( (n = 8) \). Operative plus interstage mortality was identical in each group at 21%. The combined duration of intubation, ICU and hospital length of stays for both the initial palliation plus the second stage repair (simple cavopulmonary connection in mBTS patients vs. the comprehensive stage II palliation in the hybrid patients) was significantly shorter for the hybrid patients. The 1-year outcome transplant-free survival was not different between groups (Norwood with mBTS [69.2%] vs. hybrid [73.7%]). A later follow-up by the same group with a larger group of patients (Norwood \( [n = 43] \) vs. hybrid \( [n = 32] \)) reported that freedom from death or transplant at 3 years after stage II palliation was 80.4% for patients who underwent a Norwood procedure compared with 85.6% for patients who underwent a hybrid procedure \( (P = 0.66) \) [28].

### Anesthetic considerations

The diagnosis of HLHS is most frequently made in utero, as previously noted. A postnatal transthoracic echocardiogram is performed as soon as the infant is stabilized, to confirm diagnosis, assess the atrial septum for restriction, the AV valve for regurgitation, and to evaluate AA vs. AS, and RV size and function. Patients with a restrictive atrial septum may require urgent or emergent intervention, with either balloon atrial septostomy or early surgery. Cardiac catheterization is rarely performed, and additional imaging (i.e., computed tomography [CT] or magnetic resonance imaging [MRI]) is also rarely required unless anatomic questions remain. Chest radiograph is followed daily to assess heart size and status of the pulmonary vasculature. Standard laboratory examination includes complete blood count, coagulation studies, measurement of serum electrolytes, blood urea nitrogen, creatinine and glucose, as well as blood type and cross-match. Umbilical catheters are left in place and utilized for the surgery if in correct position. As noted earlier, most HLHS patients in the recent era are not ventilated mechanically in the preoperative period, as spontaneous ventilation on room air is desirable. Most patients develop progressive tachypnea and retractions over the first few days of life as PVR decreases and pulmonary interstitial edema ensues.
Although the vast majority of neonates presenting for stage I reconstruction (i.e., Norwood or Sano operation) receive an intravenous (IV) induction of anesthesia, virtually any anesthetic agent can be used for this purpose, with careful attention to the hemodynamic consequences of the technique selected. We prefer the pheynylpiperidine-based synthetic opioids (i.e., fentanyl) because they blunt the endogenous catecholamine response to noxious stimuli at doses that are usually tolerated hemodynamically [29–31]. However, even with these hemodynamically “neutral” agents, large doses may result in significant cardiovascular changes, such as bradycardia and hypotension. These observations suggest that the neonate with HLHS requires some endogenous catecholamine release to sustain satisfactory hemodynamics. Unfortunately, this threshold dose that separates “sufficient” from “excessive” varies between patients, necessitating individual titration to arrive at the optimal dose.

Although clinical research conducted over two decades ago popularized the view that very large doses of opioid analgesics should be administered perioperatively to effect stress hormone suppression in neonates undergoing cardiac surgery [32], recent efforts to duplicate these findings have not confirmed the original results [33]. The latter demonstrated that very large doses of fentanyl did not completely suppress release of endogenous catecholamines, even in combination with benzodiazepine infusions. Additionally, outcome measures were no different in any of the study groups. We typically employ total intraoperative fentanyl doses between 10 and 20 μg/kg followed by a fentanyl infusion (1–2 μg/kg/hour) begun postoperatively in the cardiac ICU with the target being tracheal extubation on the first postoperative day. Strategies described in other institutions include a higher total dose of fentanyl (i.e., 50–100 μg/kg) and the addition of low-dose volatile anesthetics such as isoflurane – benzodiazepines, ketamine, and even dexmedetomidine have been described as components of a balanced anesthetic approach to initial palliations for HLHS [34].

Management of the airway and ventilation assumes great importance during induction of anesthesia. Given the propensity for the majority of neonates with HLHS to exhibit excessive PBF, the anesthesiologist must take care not to employ ventilatory maneuvers that lower PVR, such as hyperventilation with high concentrations of oxygen. In an infant with typical HLHS physiology, one might initiate manual ventilation with air or a low concentration of supplemental oxygen. The extent to which the anesthesiologist adjusts FiO₂ prior to laryngoscopy would depend upon the magnitude of hemodynamic response to the initiation of controlled ventilation. Infants who demonstrate significant reduction in systemic arterial pressure despite low FiO₂ may not tolerate prolonged exposure to high FiO₂ without deleterious hemodynamic consequences. Means of increasing PVR should be available in the OR. We favor inspired CO₂ for several reasons. It tends to augment systemic arterial pressure immediately and does not require neutralization of all safety systems designed to avoid delivery of a hypoxic gas mixture. Also, as a gas of some historical importance in anesthesia delivery systems, it is available with flow meters in appropriate clinical ranges. Tabbutt et al., in a clinical comparison of intubated, paralyzed, and anesthetized neonates with HLHS, demonstrated that inspired CO₂ proved consistently more effective than hypoxic gas mixtures at increasing indices of systemic output, including systemic arterial pressure and oxygen delivery [6].

Intraoperative monitoring consists of continuous invasive arterial pressure in addition to standard cardiovascular, respiratory, and temperature monitors. Whenever possible, umbilical arterial lines are utilized in patients during first stage surgery in order to preserve access for future interventions. In order to minimize the hazard of thrombosis in the central thoracic veins in all single-ventricle patients, we employ direct transthoracic atrial lines in lieu of percutaneous jugular or subclavian central venous pressure catheters. In addition, an umbilical venous catheter positioned in the orifice of the superior vena cava (SVC) at the time of surgery serves as a valuable monitor of mixed venous oxygen saturation, enabling more precise assessment of systemic CO and Qp:Qs [6,35,36].

At the termination of CPB, the physiologic goals are identical to those expressed preoperatively, although the proclivities are quite different. The pulmonary circulation now resides at either the distal end of a restrictive prosthetic systemic-to-pulmonary shunt or an RV–PA tube. A variety of subtleties in the technical execution of either shunt, relief of atrial obstruction, and pre-existing condition of the pulmonary circulation can render the ultimate physiology somewhat unpredictable. Technical issues of graft insertion, proper graft size (particularly in the neonate under 2.0 kg), and the ability to delineate the etiology of insufficient PBF on termination of CPB introduce additional complexities in a number of patients where a Sano modification has been performed.

Measures to assure a clear airway and complete re-expansion of the pulmonary parenchyma are performed in the terminal phases of rewarming on bypass. The magnitude of reduction in the mean systemic arterial pressure that occurs with trial opening of the shunt during the terminal phase on CPB can provide qualitative insights into what PVR one might expect in the early post-bypass period. Initial ventilatory support should be adjusted accordingly. In general, we begin with a pattern of ventilation designed to result in low-normal PaCO₂ and an FiO₂ between 0.6 and 1, recognizing that adjustments become necessary in all patients, as indicated by the individual infant’s physiology. In addition, the physiology typically demonstrates dynamic change over time, requiring continuous surveillance and further adjustment. Assuming a technically satisfactory repair and no unusual risk factors, PVR typically falls in the first few hours after surgery. Even with a perfect technical result, the Norwood operation does not result in any reduction of the volume or pressure burden placed on the single ventricle,
as the physiology of parallel systemic and pulmonary circulations with a Qp:Qs of 1.0 remains the objective throughout the postoperative period. Yet the heart incurs the cost of insults related to CPB, cessation of coronary perfusion, and DHCA. This may account for the cardiovascular frailty exhibited by these infants in the early postoperative period. However, in the absence of major deficiencies in myocardial protection or persistent anatomic residua, such as significant aortic arch obstruction, coronary compromise, or valvular insufficiency, myocardial dysfunction can usually be ameliorated with relatively modest doses of inotropic agents (e.g., dopamine at 3–5 μg/kg/min) and vasodilation. In a postoperative time course typical for many neonates and young infants who have undergone major cardiac interventions, myocardial performance may deteriorate in the first 6–12 hours postoperatively before it begins to improve. As a result, we routinely take measures to reduce metabolic demands by provision of continuous neuromuscular relaxant (vecuronium 0.035–0.1 mg/kg/hour) and opioid (fentanyl 1–2 μg/kg/hour) infusions. Infants demonstrating increased SVR during rewarming on CPB often receive a loading dose of milrinone at that time. Zuppa et al. described the pharmacokinetics of milrinone in 16 neonates with HLHS given a loading dose of milrinone on CPB at the time of rewarming [37]. These investigators recommended a loading dose of 100 μg/kg, followed by initiation of an infusion of 0.2 μg/kg/min within 90 minutes of the bolus dose to achieve and maintain plasma concentrations similar to those reported in other therapeutic settings. No data exist to guide bolus and/or infusion doses when milrinone is begun after termination of CPB. Modified ultrafiltration (MUF) conducted immediately following CPB has been demonstrated to exert beneficial effects upon hematocrit, hemodynamics, hemostasis, pulmonary function, and central nervous system recovery [38–42]. Perioperative weight gain is reduced significantly, as are certain inflammatory mediator levels. Whenever possible, we conduct MUF at the termination of CPB following stage I reconstruction. Occasionally, the position of the bypass cannulae or the continuous flux of blood through the MUF circuit results in unfavorable hemodynamic changes precluding completion of the filtration. In 99 consecutive patients undergoing stage I between September 2000 and August 2002, all tolerated the hemodynamic perturbations of MUF [43].

Stage I reconstruction requires substantial suture lines in creation of the neo-aorta, thus rapid restoration of normal hemostasis represents an important early postoperative objective. Following completion of MUF, and once satisfied with the technical and physiologic result of the repair, heparin effect is reversed with protamine. Given the risk factors that jeopardize platelet number and function, including deep hypothermia and profound dilution of circulating volume on CPB [44], replacement of blood loss with fresh whole blood (<48 hours old) restores hemostasis more effectively than other blood products [45]. Fresh whole blood replacement also serves to minimize donor exposure to these patients who are anticipated to require a minimum of three open heart surgical interventions. Despite the theoretical advantages of fresh whole blood, other studies have not demonstrated a benefit of this strategy relative to reconstituted whole blood [46]. In addition, fresh whole blood is not available in the great majority of institutions. A recent publication demonstrated that a reconstituted fresh whole blood bypass prime, consisting of packed red blood cells, fresh frozen plasma, and platelets from the same donor, less than 7 days old, followed by a second such unit given after bypass, reduced bleeding in infants undergoing surgery compared with standard blood component therapy [47]. Should these measures fail to achieve adequate hemostasis despite elimination of all surgical bleeding sites, laboratory testing should be conducted to direct component therapy at those elements of the hemostatic pathway most likely to be impaired: platelet and fibrinogen replacement.

No systematic data have been published specifically examining procoagulant medications in infants undergoing stage I reconstruction, and there are only sparse data examining neonates as a group. Antifibrinolytic therapies have demonstrated efficacy in infants and children following heart surgery, but data in neonates continue to be very limited [48–51]. The lysine analogs epsilon aminocaproic acid and tranexamic acid appear to have comparable efficacy [48,51], and extensive experience implying safety, although there are insufficient pediatric follow-up data to validate their safety scientifically. Their benefit is probably most notable in high-risk patient populations, such as cyanotic patients undergoing extensive operations. While aprotinin, a serine protease inhibitor that acts as an antifibrinolytic agent with anti-inflammatory properties, has demonstrated effectiveness comparable to other antifibrinolytics in infants and children [52], this agent was voluntarily removed from the market when it was linked to greater 5-year mortality following coronary bypass grafting [53]. Recombinant activated factor VII (rFVIIa) has been used as rescue therapy in infants and children, including neonates undergoing stage I reconstruction, following cardiac surgery when conventional correction of postoperative coagulopathy with blood product transfusions fails to control hemorrhage [54,55]. While rFVIIa can be effective in controlling intractable hemorrhage, caution is warranted, as systematic studies of safety and efficacy have not been conducted [56]. Among procoagulant therapies, rFVIIa is uniquely capable of producing a hypercoagulable state that poses risks to certain surgical repair elements such as prosthetic shunts. Prompt control of hemostasis resulting in reduced transfusion requirement can be associated with a reduced need for re-exploration for bleeding. Re-exploration in patients younger than 2 years undergoing complex surgery at our institution, which includes all single ventricle patients, was reduced from 3% to 0.8% following adoption of the routine use of fresh whole blood. Cardiac tamponade can easily occur from a small quantity of mediastinal blood.
accumulated in the early postoperative period before bleeding has completely ceased. Continuous removal is essential because blockage easily occurs in the relatively small mediastinal drainage tubes of these neonates. A technique of active, continuous aspiration of accumulating blood from the mediastinum has virtually eliminated this complication [57].

Common problems in the early post-bypass period
Excessive hypoxemia represents one of the more commonly encountered problems in the early post-bypass period. Although inadequate Qp:Qs is generally the assumed cause, factors that impair systemic oxygen delivery and thereby reduce mixed venous oxygen saturation are now known to be more common than previously believed [35,58–60]. One typically observes a progressive increase in systemic oxygen saturation during MUF; for example, probably due to the impact that hemococoncentration and the resulting increased oxygen delivery have upon mixed venous oxygen saturation. Thereafter, measures directed at maintaining hematocrit above 40–45% may alleviate excessive demands placed upon the recovering heart to increase systemic output. The distinction between systemic hypoxemia due to low Qp:Qs, low pulmonary venous oxygen saturation, or low mixed venous saturation is a critical one, as the therapies are diametrically different. Measures designed to reduce PVR will impose a further volume load on a heart already struggling to provide marginal systemic perfusion. Patients demonstrating low SvO2 are better served with therapies that promote systemic output, such as inotropic agents or vasodilators.

Similarly, those with low pulmonary venous oxygen saturation require a strategy of ventilatory support designed to reduce atelectasis and promote gas exchange in impaired alveoli. Unfortunately, the latter diagnosis is rarely made definitively in the OR or cardiac ICU, as blood sampling from the pulmonary veins presents logistic challenges. Intraoperatively, expectant measures directed at expansion of the lungs and maintenance of normal functional residual capacity (FRC) usually suffice to avoid pulmonary vein desaturation. Among the three etiologies of persistent systemic hypoxemia, this was believed to be the least common, but a recent series found pulmonary vein desaturation in as many as 30% of patients [61].

When systemic hypoxemia occurs due to low Qp:Qs, other manifestations provide supporting evidence. Trial opening of the systemic-to-pulmonary artery shunt during the latter phases of rewarming on CPB fails to demonstrate significant drop in the mean systemic arterial pressure, and early post-bypass hemodynamics reveal a relatively narrow pulse pressure and/or high diastolic pressure. A substantial discrepancy exists between arterial and end-tidal CO2 measurements. These suggestive pieces of inferential evidence can be confirmed by aortic Doppler flow analysis or calculation of a Fick ratio using oxygen saturation determinations. Most commonly, diminished PBF reflects a subtle technical aspect of the arch reconstruction, innominate artery dimension, or the mBT shunt. However, certain patient subsets exhibit profound abnormalities in the pulmonary vasculature that result in excessive PVR elevations. Neonates with HLHS routinely demonstrate extremely high and volatile PVR when born with severe pulmonary venous obstruction due to intact atrial septum without alternative decompressing veins. Even the typical HLHS anatomic constellation is associated with marked abnormalities in the number and muscularization of the pulmonary vasculature by pathologic examination [62]. Hypotheses attribute these changes to chronic fetal pulmonary venous obstruction [63]. One can speculate that these changes become more extreme in the context of the marked obstruction caused by HLHS with intact atrial septum. Fetal echocardiography has confirmed alteration in pulmonary venous flow pattern in relation to the magnitude of restriction at the atrial septum [64].

In the context of hypoxemia due to low Qp:Qs, interventions fall into three categories: surgically related technical issues, pulmonary vasodilation, and systemic vasoconstriction. In the subgroup of patients expected to have unusually elevated PVR, modifications in surgical technique might entail placement of a larger shunt or shunt interposition between a larger systemic vessel (e.g., aorta) and PAs. Pulmonary vasodilator therapy includes the strategies one might employ in any patient demonstrating elevated PVR, such as oxygen, moderate hyperventilation, normothermia, alkali, and nitric oxide [65–67]. Should those measures prove insufficient to result in adequate PBF, the focus might be expanded to include measures designed to increase the driving pressure across the shunt, using higher doses of inotropic infusions or even vasoconstrictors. The latter necessitates careful monitoring to avoid jeopardizing perfusion to other vital organs.

Depressed myocardial performance represents another potential problem in the early post-bypass period. As mentioned previously, some degree of myocardial dysfunction typically occurs following this stage I palliation, as no hemodynamic benefit is achieved that offsets the cost of CPB and an ischemic interval. When this dysfunction becomes more significant than usual, specific causes should be sought. Even in the context of the typical conduct of stage I reconstruction, the presence of AA can make routine myocardial protection measures, such as the infusion of cardioplegia solutions, challenging, and thus inadequate myocardial preservation represents one potential cause for persisting or excessive myocardial depression.

Technical considerations represent the predominant cause of myocardial dysfunction following this complex intervention. One of the most intricate aspects of this procedure is the reconstruction of an aortic arch in such a way that the small ascending aorta, which principally serves to provide coronary flow, is not compromised. This subtle finding may not become evident until the cardiac volume is restored in anticipation of terminating CPB. Residual hemodynamic derangement represents another potential
cause of myocardial dysfunction. Given that under the best of circumstances, one emerges from the Norwood operation with no appreciable hemodynamic benefit, one would expect a result with newly imposed volume or pressure loads to be poorly tolerated. Examples of such findings would include residual aortic arch obstruction, AV valve dysfunction, and/or semilunar valve obstruction or regurgitation.

Metabolic disturbances can also result in significant myocardial dysfunction. A fragile RV struggling to cope with significantly increased volume output demands at systemic pressure is perhaps more susceptible to what might otherwise be modest metabolic disturbances. As such, one should track and address those variables that have an impact upon myocardial performance, such as ionized calcium levels and the presence of lactic acidosis. The rapid administration of blood products containing calcium-binding drugs, high levels of potassium and lactic acid, as well as other vasoactive mediators, can result in an acute, profound deterioration in cardiac performance in the early postoperative period. In our experience, myocardial performance will deteriorate when the arterial pH falls below 7.3 and may contribute to further reduction in Qs. The administration of IV bicarbonate, calculated to completely eliminate the base deficit, often exerts a beneficial effect on both myocardial performance and Qs. In addition to the inherent cardiac sensitivity, inescapable anatomic peculiarities accentuate this vulnerability. Blood carrying the transfused products from the systemic venous circulation enters the RV and is directed immediately to the reconstructed aorta, whereby the first branch is the coronary circulation. Thus, constituents of the transfused blood (e.g., citrate, potassium, lactate) infused into the venous circulation arrive at the coronary arteries with greater speed and concentration than might have occurred had they been dissipated over the course of the pulmonary vasculature before entering the aorta. This effect is further accentuated if central venous catheters are employed to infuse the blood product. We abide by a protocol whereby blood transfused via central lines or rapidly through peripheral catheters is either less than 7 days of age or consists of washed packed cells.

Arrhythmias most commonly occur as manifestations of the problems described previously. When they become manifest early in the process of rewarming on CPB, coronary insufficiency represents the most common cause, particularly if the arrhythmia is ventricular in origin. Metabolic disturbances produce the same qualitative rhythm changes seen in normal hearts, although the manifestations might be more extreme. Given the predominantly extracardiac nature of the Norwood procedure, acquired heart block rarely follows this operation unless it existed preoperatively. On rare occasions, a patient presents with HLHS and a primary arrhythmia, such as Wolf–Parkinson–White syndrome.

Excessive PBF may complicate the early postoperative period; however, this diagnosis should be entertained cautiously. In many instances, the apparent excess PBF really reflects a relative imbalance with respect to significantly diminished systemic CO (Qs). The latter should be specifically excluded and addressed before invoking extreme measures to restrict PBF. Of course, subtle technical differences in the conduct of the operation can result in an anatomic propensity to an excessive Qp:Qs, and this can, in turn, jeopardize systemic perfusion. Such patients typically exhibit an extremely wide pulse pressure or low diastolic pressure, reflecting pulmonary “run-off.” If myocardial performance otherwise appears robust, the specific measures employed to increase PVR preoperatively are appropriate in this setting. In most patients, this condition dissipates as the infant recovers from surgery. Should the problem persist beyond the first postoperative day, a cardiac catheterization should be considered to evaluate the need for further surgical intervention aimed at diminishing PBF.

The subset of patients who demonstrate inability to separate from CPB or refractory cardiac dysfunction postoperatively may benefit from utilization of ECMO as a support strategy. Ungerleider et al. have advocated the routine use of mechanical ventricular assistance in all patients following stage I reconstruction, reporting 89% survival to hospital discharge [68]. More recently, a retrospective review of patients who required non-elective institution of ECMO in the OR or the cardiac ICU revealed a 38.8% survival to hospital discharge. Significantly, all patients with acute shunt thrombosis were early survivors. Risk factors for mortality in this patient population included longer CPB time, need for institution of ECMO <24 hours postoperatively, cannulation via the chest, and longer duration of ECMO support [69].

The volume work of the single ventricle after stage I reconstruction is equal to the sum of the systemic and pulmonary blood flows (Qp + Qs). After a period of maturation of the pulmonary vasculature, systemic venous return may be directed to the pulmonary arteries, thus placing the two circulations in series. When Fontan’s operation was uniformly undertaken 12–18 months after stage I, an operative mortality of 16–40% occurred [70]. The most common cause of early death was low CO associated with tachycardia, low systolic and diastolic blood pressures, and high ventricular end-diastolic pressures. The majority of patients with signs of low CO demonstrated echocardiographic evidence of an abrupt change in ventricular geometry that resulted in a small, thick-walled cavity with a low diastolic volume when compared with the preoperative state. Although systolic shortening appeared normal, the ventricular compliance was diminished. The physiologic result was impaired diastolic function of the ventricle resulting in increased end-diastolic pressure. The resulting increase in pulmonary venous pressure impeded PBF, thereby reducing systemic output. Retrospective analysis of the data available preoperatively proved insufficient to predict those children who would develop physiologically important reduction of ventricular compliance associated with rapid contraction of end-diastolic volume following single-stage Fontan.
KEY POINTS: HYPOPLASTIC LEFT HEART SYNDROME

- Preoperative stabilization of HLHS requires infusion of PGE1 to maintain ductal patency, and measures to balance Qp:Qs to close to 1:1; elevating PVR with room air ventilation and mild hypercarbia are often required.
- Stage I palliation involves reconstructing the hypoplastic aorta, with the pulmonary valve becoming the neo-aortic valve and coronary perfusion dependent on a technically sound anastomosis.
- Pulmonary blood flow is supplied by either a systemic-to-pulmonary shunt or a RV-to-pulmonary shunt; mid- and longer-term outcomes are equivalent with either shunt.
- Hybrid palliation involves a non-bypass surgery to place pulmonary artery bands combined with interventional catheterization to stent the PDA and possibly stent the ASD; a comprehensive stage II palliation involving aortic arch reconstruction is done at the time of the superior cavopulmonary anastomosis.
- Interstage mortality continues to be an issue, currently at about 10–12%.

Tricuspid atresia

Incidence, anatomy, and natural history

Tricuspid atresia is defined as a complete absence of the tricuspid valve, with no communication between the RA and the RV. This defect results in hypoplasia of the RV with absent inlet portion, incompletely formed trabecular portion, and an RV comprised mainly of an infundibular portion. TA also results in a functionally single LV (Figure 25.6) [20]. TA accounts for approximately 0.5–1% of CHD at birth [71], and is classified as type I, II, or III (Figure 25.7).

- **Type I TA** is the most common (70–80% of patients) and has normally related great arteries. Type I TA is further subdivided into:
  - Type Ia – intact ventricular septum with pulmonary atresia
  - Type Ib – small ventricular septal defect (VSD) and pulmonary stenosis
  - Type Ic – large VSD without pulmonary stenosis

- **Type II TA** (12–25% of patients) has transposition of the great arteries (TGA) and is further divided into:
  - Type IIa – VSD with pulmonary atresia
  - Type IIb – VSD with pulmonary stenosis
  - Type IIc – VSD without pulmonary stenosis

- **Type III TA** is uncommon at 3–6% of TA patients, and is used to classify TA with complex associated malformations such as AV septal defect or truncus arteriosus.

In TA the systemic venous blood cannot flow directly into the RV; it must pass from RA to LA through an ASD or stretched PFO and mix completely with pulmonary venous blood; and then to the LV, and across a VSD to the small RV infundibulum; from there blood flows into the pulmonary arteries with TA and normally related great vessels. Obstruction to PBF with a restrictive VSD or pulmonic stenosis results in significant cyanosis.

Without intervention, survival to 1 year of age in patients with TA is as low as 10% [71]. Longer-term survival and symptomatology in the pre-Fontan era depended on the degree of obstruction to PBF; the earliest operations for TA consisted of systemic-to-pulmonary artery shunts. TA was the first single-ventricle lesion to have the Fontan principle applied; there are many long-term adult survivors of the early Fontan era from the 1970s (see later). TA patients with balanced systemic and PBFs have a mild degree of pulmonic stenosis, which prevents the development of pulmonary vascular disease, and cyanosis is not severe in infancy, permitting longer-term survival without intervention.

Diagnosis of TA is made by echocardiography, frequently in utero. Postnatal transthoracic echocardiogram is sufficient to define the anatomy and plan surgical intervention, if required, in almost all cases of TA. Two-dimensional and color Doppler ultrasound can define very clearly the size of the VSD and the RV, relation of the great vessels, degree of pulmonic stenosis, presence...
Chapter 25 Anesthesia for the Patient with a Single Ventricle

Tricuspid atresia variants (see the text for a complete explanation). Percentages in parentheses refer to the approximate incidence of each type. (Source: Jacobs [72]. Reproduced with permission of Wiley.)

and size of a PDA, and level of flow in across all of these areas. It can also define other associated cardiac anomalies. Cardiac catheterization, MRI, and CT are rarely needed in the neonatal period but may be used infrequently to define unusual anatomy.

Pathophysiology of TA

In type I TA, the great vessels are normally related, systemic and pulmonary venous blood mix completely in the LA, and the degree of cyanosis depends on the amount of PBF, which in turn depends on the size and restriction to flow of the VSD, and pulmonary outflow. TA type Ib (small VSD and pulmonary stenosis) is often dependent on the PDA to maintain adequate oxygen saturation; a closing PDA can result in profound cyanosis, and PGE₂ should be infused in these patients. The VSD may be of adequate size in early infancy, but as the heart grows and CO increases, the size of the VSD may become inadequate, resulting in increased cyanosis. In TA type Ic (large VSD without pulmonary stenosis), PBF is unrestricted through the VSD and pulmonary outflow tract, resulting in less cyanosis, but with increased Qp:Qs and pulmonary overcirculation, and congestive heart failure (CHF) may develop, necessitating diuretic therapy.

With type II TA, the great vessels are transposed, and because the LV ejects directly into the PA, these patients frequently develop pulmonary overcirculation and CHF in the first few weeks of life. This scenario is common in type II TA, because obstruction to PBF is unusual. If the VSD is restrictive in type II TA, systemic blood flow antegrade across the aortic valve will also be diminished, resulting in systemic hypoperfusion and shock that is worsened as the PDA narrows in the first few days of life; PGE₁ may be necessary to maintain the PDA. Table 25.1 summarizes the anatomic classification, incidence, and pathophysiological features of TA.

Surgical and transcatheter approaches and outcomes

Neonatal surgical approaches in TA depend on the anatomic classification and the pathophysiologic consequences [72]. Type Ib and IIb patients often have mild restriction to PBF and are not cyanotic; yet neither do they develop CHF, and they are thus “well balanced,” possibly not requiring neonatal surgical intervention. These patients are followed over the first several months of life for increasing cyanosis, and normally undergo the SCPA as their first operation, before 6 months of age. Type Ia and IIa patients have pulmonary atresia and are maintained on PGE₁ until they undergo a surgical mBTS; type Ic and IIc patients often develop CHF in the first weeks of life and may require PA banding to restrict PBF. Type II TA patients with restrictive VSDs or subaortic obstruction are PDA-dependent for adequate systemic circulation. These patients may undergo a “palliative” arterial switch operation (ASO) to place the aorta so that the unobstructed LV ejects into it; the VSD may need to be enlarged in this case to prevent profound cyanosis [73] (see Chapter 24 for detailed discussion of the ASO). If the VSD is unrestricted, yet subaortic obstruction exists, they may undergo a Damus–Kaye–Stansel (DKS) operation, which is an end-to-side anastomosis of the ascending aorta to the main PA, which provides relief of the subaortic obstruction. PBF is provided either by an mBTS or RV–PA shunt, and the operative and anesthetic considerations for this surgery are very similar to that for the Norwood stage I palliation of HLHS. Figure 25.8 presents surgical options in the case of TA type II with significant subaortic stenosis.

Anesthetic considerations

Pulmonary artery banding

These patients are young infants with varying degrees of CHF; cyanosis is mild and they are often receiving
### Table 25.1 Anatomic and physiologic classification of tricuspid atresia

<table>
<thead>
<tr>
<th>Type</th>
<th>Major anatomic features</th>
<th>Incidence</th>
<th>Major pathophysiologic features</th>
<th>Neonatal surgical approach</th>
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<tbody>
<tr>
<td>Type I: Normally related great arteries</td>
<td></td>
<td>70–80%</td>
<td>Cyanosis</td>
<td>CHF</td>
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<td>Large VSD, no PS</td>
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<td>Type II: Transposition of the great arteries</td>
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<td>Ib</td>
<td>VSD with PS</td>
<td>++</td>
<td>−</td>
<td>Yes if VSD restrictive</td>
</tr>
<tr>
<td>Ic</td>
<td>VSD no PS</td>
<td>+</td>
<td>++</td>
<td>Yes if VSD restrictive</td>
</tr>
<tr>
<td>Type II: Transposition of the great arteries with restrictive VSD or subAS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Type III: Normally related or transposed great arteries with other complex cardiac lesions</td>
<td></td>
<td>3–6%</td>
<td>+ to +++</td>
<td>− to ++</td>
</tr>
</tbody>
</table>

PS, pulmonic stenosis; CHF, congestive heart failure; VS, ventricular septum; VSD, ventricular septal defect; mBTS, modified Blalock–Taussig shunt; DKS, Damus–Kaye–Stansel operation; ASO, arterial switch operation; subAS, subaortic stenosis. +, mild; ++, moderate; ++++, severe; −, no effect.

Diuretic therapy, and are tachypneic with poor feeding and growth. Preoperative evaluation consists of thorough physical examination and history, chest radiograph to assess heart size and the degree of pulmonary overcirculation, baseline pulse oximetry and hemoglobin to assess the level of chronic cyanosis, and serum electrolyte values to determine any abnormalities from chronic diuretic therapy. A complete transthoracic echocardiogram is sufficient to determine anatomy and functional characteristics, including any mitral valve regurgitation. Cardiac rhythm disturbances are unusual at this stage, but 12- or 15-lead ECG is helpful to exclude arrhythmias.

After standard monitors are placed, induction of anesthesia can be achieved via inhalation or IV induction with any of a variety of agents; oro- or nasotracheal intubation is accomplished, and arterial access is achieved for monitoring. Central venous access is used by some anesthesiologists; it is important to avoid the superior vena caval circulation for these catheters, as the SVC will be utilized later for the SCPA, and thrombosis in the SVC in a small infant with a single functional ventricle is a serious problem that may preclude the SCPA. The femoral venous route is chosen instead. Other institutions utilize a transthoracic RA line; or, if two larger-bore peripheral IVs are present, others would not place central venous catheters at all. An important anesthetic principle for the PA banding procedure is that the anesthetic must achieve a baseline state that is neither too deep nor too light at the time of the PA banding, so that the tightness of the band is appropriate for the patient. In addition, FiO₂ and PaCO₂ at the time of placement of the band need to be near baseline for the patient, i.e., low FiO₂ of 0.30 or less, and PaCO₂ which is often in the mid-40s mmHg due to the metabolic alkalosis from diuretic therapy, and the mild state of respiratory insufficiency from CHF. Transesophageal echocardiographic guidance is used by many centers for PA banding.

The operation is normally performed through a median sternotomy without CPB, and after dissection the surgeon places a thin cotton tape, similar to umbilical tape, around the main PA, being careful not to impinge on branch PAs or on the pulmonary valve. Many surgeons employ a formula derived by Albus et al. [74] to determine the initial circumference of the PA band. Infants with simple two-ventricle defects without intracardiac mixing disorders (isolated VSD or AV septal defect) have an initial PA band circumference of 20 mm + 1 mm for each kg body weight. In modern practice, PA banding for this indication is rarely performed; a complete repair is preferred. Infants with bi-directional mixing disorders, which includes all infants with TA and other forms of univentricular heart receiving PA bands, have an initial PA band circumference of 24 mm + 1 mm for each kg body weight. In modern practice, PA banding for this indication is rarely performed; a complete repair is preferred. Infants with bi-directional mixing disorders, which includes all infants with TA and other forms of univentricular heart receiving PA bands, have an initial PA band circumference of 24 mm + 1 mm for each kg body weight. PA band tightness is adjusted by various methods: the primary method is to assess the change in pulse oximeter saturation, and the measured arterial PaO₂ in saturation, after placement of the band, with an SpO₂ of 75–85% and a PaO₂ of approximately 40–45 mmHg normally targeted. Echocardiographic peak velocity (V) across the PA band of approximately 3 m/s is a frequent goal; this
corresponds to a pressure gradient of 36 mmHg using the modified Bernoulli principle (peak velocity = $4V^2$). Finally, direct pressure measurement in the surgical field is utilized by some institutions; a PA pressure distal to the PA band that is about one-third of systemic arterial pressure (range, 25–50%) is a frequent goal. The PA band is adjusted temporarily with surgical clips, blood gas measurements can be obtained after steady state conditions are achieved, and the band permanently secured with non-absorbable sutures. A PA band that is too tight will produce profound cyanosis and bradycardia; one that is too loose will produce little change from baseline conditions. The final circumference of the PA band is often determined by surgical judgment – hence the importance of achieving and maintaining steady-state anesthetic and ventilatory conditions. As the patient emerges from anesthesia, CO changes, and the relative tightness of the band changes; also because the patient is in a period of rapid somatic and cardiac growth, they often “outgrow” the PA band and cyanosis increases over time. Despite research into “adjustable” PA bands over the past several decades, this technology is not available in the US. Almost
all of these infants will undergo the SCPA within a few months, and so this issue usually is not applicable in the infant single-ventricle population. Inotropic support is not usually necessary. The PA band placement mechanically increases the resistance to flow through the PA, and because of complete intracardiac mixing, more blood flow is directed out to the aorta, and systemic arterial pressure often increases significantly after placement of a PA band. Occasionally a vasodilator such as sodium nitroprusside is necessary to control blood pressure. After surgery, the trachea can often be extubated in the OR, or within the first few hours of admission to the ICU.

**Systemic to pulmonary artery shunt**

Tricuspid atresia patients with pulmonary atresia or significant pulmonic stenosis presenting for mBTS are usually neonates receiving PGE, to maintain the PDA and avoid profound cyanosis. Occasionally, an older infant with closed ductus arteriosus and profound cyanosis will present for this operation. This surgery is normally done without CPB; a right thoracotomy or median sternotomy approach can be utilized. The anesthetic considerations for mBTS are presented in detail in Chapter 23.

**Damas–Kaye–Stansel operation and palliative ASO**

As noted earlier, the DKS operation is performed for TA variants with significant subaortic or aortic obstruction, or with a restrictive VSD. The anesthetic considerations are very similar to those for Norwood stage I palliation, discussed earlier. Because the single functional ventricle is an LV, and because the aortic valve is not atretic and the coronary artery circulation is not as tenuous as in HLHS, these patients are generally expected to have a more stable pathophysiologic condition after DKS, compared with the Norwood stage I palliation. The palliative ASO has many anesthetic considerations in common with the standard ASO for D-TGA with two ventricles (discussed in Chapter 24). The major difference, of course, is that TA still remains, and PBF needs to be adequate after the ASO, often requiring enlargement of the VSD, or possibly a mBTS.

**Other forms of univentricular hearts**

Besides HLHS and TA, there are a number of other forms of univentricular hearts, with a single functional systemic ventricle, that present in the neonatal period and may require a neonatal surgical palliation [72,75,76]. These patients virtually always undergo the staged palliation with SCPA at 3–6 months, and Fontan completion at 18 months to 3 years of age. Although collectively accounting for only 1–2% of all CHD patients diagnosed at birth, the congenital cardiac anesthesiologist encounters these patients relatively frequently for anesthetic care for staged surgical palliation, catheterization procedures, imaging procedures such as MRI, and non-cardiac surgery. Therefore, it is important to be familiar with these additional lesions. Table 25.2 summarizes these other univentricular heart variants presenting for infant cardiac surgery.

**Double inlet ventricle**

In double inlet ventricle, both atria connect only to a single ventricular chamber, either by a common AV valve or by two separate AV valves. The additional ventricle is hypoplastic; in some cases there can be partial connection to this rudimentary ventricle by a straddling AV valve. The single functional ventricle can be an LV (most common), RV, or a ventricle of indeterminate morphology (rare). The rudimentary ventricle lacks an inlet portion most commonly; the outlet chamber can be absent as well. A VSD or bulboventricular foramen is normally present and may restrict flow to the outlet chamber and great vessel attached to it. The double inlet LV is the most common subtype, with a right-sided anatomic LV and ventricular arterial discordance, i.e., transposition of the great vessels (Figure 25.9). The neonatal surgical palliative approach will depend on the exact anatomy and pathophysiologic consequences. Patients with significant restriction to PBF because of restrictive bulboventricular foramen may require mBTS; those with aortic valve and aortic hypoplasia may require a DKS operation or palliative ASO (see earlier); and those with no restriction to either pulmonary or aortic outflow may require PA banding. The anesthetic considerations for these procedures are discussed earlier in the chapter.

**Mitrail atresia with VSD**

Mitrail atresia with VSD denotes absence of the left AV valve connection from the LA to the LV, resulting in a functionally univentricular heart with a dominant RV, and a hypoplastic LV connected to the RV via a VSD or bulboventricular foramen. Both the aorta and PA may arise from the RV, or the aorta can arise from the small LV, in which case the aorta is often hypoplastic as well. This arrangement can be considered a variant of HLHS. Neonatal palliation often consists of placement of a PA band in patients with unrestricted flow through both great
Table 25.2  Other types of univentricular heart variants presenting for neonatal cardiac surgery

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Morphology of systemic ventricle</th>
<th>Associated cardiac findings</th>
<th>Neonatal surgical palliation options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Double inlet ventricle</td>
<td>Left is most common</td>
<td>L-transposition of the great arteries; subAS; subPS</td>
<td>Damus–Kaye–Stansel; palliative ASO; PA banding</td>
</tr>
<tr>
<td>Mitral atresia with VSD</td>
<td>Right</td>
<td>Restrictive bulboventricular foramen; hypoplastic aortic arch</td>
<td>Damus–Kaye–Stansel; PA banding</td>
</tr>
<tr>
<td>Unbalanced common AV canal</td>
<td>Right or left</td>
<td>Coarctation or arch hypoplasia</td>
<td>Aortic arch repair; PA banding</td>
</tr>
<tr>
<td>Heterotaxy syndrome with single ventricle</td>
<td>Right, left, or indeterminate</td>
<td>PS; bilateral SVC; interrupted IVC; TAPVR</td>
<td>mBTS; TAPVR repair; PA banding</td>
</tr>
</tbody>
</table>

AS, aortic stenosis; PS, pulmonic stenosis; ASD, arterial switch operation; PA, pulmonary artery; VSD, ventricular septal defect; SVC, superior vena cava; IVC, inferior vena cava; TAPVR, total anomalous pulmonary venous return; mBTS, modified Blalock–Taussig shunt.

vessels; a DKS or Norwood stage I palliation operation is often necessary for subaortic obstruction or hypoplasia of the ascending aorta.

Unbalanced common AV canal
In this relatively rare defect, just as in the completely balanced, two-ventricle variety (see Chapter 21), there is a single common AV valve and a large primum ASD, along with a large inlet VSD. As the name implies, the difference is that one or the other ventricle is hypoplastic, resulting in a single functional ventricle. The right dominant unbalanced AV canal has a large RV and hypoplastic LV; the left dominant unbalanced AV canal has a large LV and hypoplastic RV. Abnormal development of aortic outflow, resulting in aortic arch hypoplasia or coarctation, may be observed in unbalanced common AV canal; however, pulmonic stenosis is unusual. Most unbalanced common AV canal lesions are obvious; however, at times one or the other ventricle can be borderline hypoplastic. Cardiologists refer to “apex-forming” or “non-apex-forming” appearance on echocardiography as one criterion – if the LV or RV apex is present in an otherwise small ventricle, this patient may be considered for two-ventricle repair. Other echocardiographic methods include calculation of the AV valve index to estimate the proportion of AV valve tissue apportioned to each ventricle.

Unbalanced AV canal patients often present in early infancy with pulmonary overcirculation and may require PA banding. Those with coarctation of the aorta or aortic arch hypoplasia may require coarctation repair or aortic arch repair, with a PA band frequently required as well. The SCPA is performed at 3–6 months.

**Single functional ventricle with heterotaxy syndrome**
Heterotaxy syndrome refers to failure of normal right–left differentiation of visceral and thoracic organs during embryological development, resulting in ambiguous or abnormal sidedness to atria and ventricles; abnormal pulmonary and systemic venous drainage, single-ventricle cardiac lesions, and abdominal organ abnormalities, such as asplenia, polysplenia, and intestinal malrotation. The paired organs, such as atria and lungs, tend to be characterized by isomerism, i.e. two mirror-image morphologically right atria on the left and right sides of the heart; two left atria; two morphologically right lungs on either side of the thorax, etc. Asplenia refers to absence of the spleen,
usually accompanied by a midline liver; polysplenic patients have multiple small spleens. Most heterotaxy syndrome patients have a functional single ventricle with, most frequently, an unbalanced complete AV canal. Pulmonary stenosis or atresia is common in this population, as is bilateral SVC, and total anomalous pulmonary venous return (TAPVR). In addition, the inferior vena cava (IVC) may be left-sided and drain into a common atrium separately from the hepatic veins, which presents problems for the surgeon during completion of the Fontan operation. The IVC is not uncommonly interrupted, without atrial connection but instead with subdiaphragmatic systemic venous drainage reconstituting above the diaphragm from collaterals, eventually draining into azygous and hemiazygous venous systems and from there to the SVC. Finally, most heterotaxy patients have intestinal malrotation and are thus prone to intestinal obstruction. Chapter 4 has an extensive discussion of the embryology and nomenclature of heterotaxy syndrome.

Heterotaxy syndrome presents a number of challenges for the perioperative teams. Asplenic patients are prone to pneumococcal and other bacterial sepsis and require lifelong penicillin prophylaxis. More than half have a univentricular heart; most commonly with a single RV. Right atrial isomerism means there is a morphologic right atrium on both sides, usually with two sinoatrial (SA) nodes, leading later in life to a propensity for atrial arrhythmias. Bilateral SVC is often accompanied by absence of the coronary sinus; this has implications for the SCPA. Bilateral trilobed lungs with a bilateral right-sided bronchus arrangement are present. Polysplenic patients have a univentricular heart less than 50% of the time, but most of these are a single RV. Interrupted IVC with azygous continuation is common. Anomalous pulmonary venous connection is common; pulmonary stenosis is less common. A persistent left SVC often drains into the coronary sinus, and left atrial isomerism is common. Because of this feature, the SA node is hypoplastic or absent, and these patients are prone to sick sinus syndrome and other bradyarrhythmias as they grow older.

Because of the great anatomical variation in heterotaxy syndrome, surgical palliation in the neonate varies widely. Because of the frequent abnormality of systemic and pulmonary venous drainage, echocardiography alone is often not sufficient to define the anatomy. Cardiac MRI, CT, or cardiac catheterization are frequently required in this population. Because TAPVR is common, repair of this condition is often the initial operation, frequently accompanied by mBTS for pulmonary stenosis or atresia, or PA band for pulmonary overcirculation. The management of TAPVR is discussed in Chapter 21. The details of the anatomic variation are very important to understand, not only for the planned surgical approach, but also for the placement of invasive arterial and central venous access catheters. The presence or absence of a spleen and intestinal malrotation can be determined by abdominal ultrasound; nuclear medicine scan (hepatobiliary iminodiacetic acid [HIDA]) is used in cases where status of the spleen is not clear. After the initial neonatal surgical palliation, virtually all heterotaxy syndrome patients undergo the staged palliation to the Fontan circulation; the concomitant anatomic abnormalities often make the surgery more difficult, and outcomes not as favorable (see later). Table 25.3 summarizes the findings in heterotaxy syndrome.

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>% with single ventricle</th>
<th>Common cardiac variants</th>
<th>Pulmonary stenosis/ atresia</th>
<th>SVC/IVC</th>
<th>TAPVR</th>
<th>SA nodes</th>
<th>Atrial morphology</th>
<th>Lung morphology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asplenia</td>
<td>&gt;50%</td>
<td>Single RV common; DORV, unbalanced CAVC</td>
<td>Common (&gt;90%)</td>
<td>Bilateral SVC common</td>
<td>Common; to extracardiac vein</td>
<td>Bilateral RA isomerism</td>
<td>Bilateral trilobed (right)</td>
<td></td>
</tr>
<tr>
<td>Polysplenia</td>
<td>&lt;50%</td>
<td>RV or indeterminate morphology</td>
<td>Less common (&lt;50%)</td>
<td>Interrupted IVC (80%)</td>
<td>To right atrium</td>
<td>Hypoplastic or absent</td>
<td>LA isomerism</td>
<td>Bilateral bilobed (left)</td>
</tr>
</tbody>
</table>

RV, right ventricle; DORV, double outlet right ventricle; CAVC, complete atrioventricular canal; SVC, superior vena cava; IVC, inferior vena cava; RA, right atrium; LA, left atrium; TAPVR, total anomalous pulmonary venous return; SA, sinoatrial.

**KEY POINTS: OTHER UNIVENTRICULAR HEARTS**

- Other forms of single systemic ventricle include double inlet ventricle, MA, unbalanced common AV canal, and single ventricle with heterotaxy.
- Neonatal palliation depends on the degree of obstruction to pulmonary or systemic blood flow, and may involve no surgery, PA banding, systemic-to-pulmonary artery shunt, or complex repairs such as DKS operation or palliative arterial switch.
- Heterotaxy is a complex malformation syndrome of abnormal sidedness of thoracic and abdominal organs; asplenia and polysplenia are the major types.
- Abnormalities of systemic and pulmonary venous return are common in heterotaxy and must be clearly defined and often need to be addressed with the neonatal palliation.
Superior cavopulmonary anastomosis

Surgical procedure

The SCPA, also termed bi-directional cavopulmonary anastomosis, or bi-directional Glenn shunt, is the second stage in the Fontan strategy for the vast majority of patients with a single functional ventricle. It may be performed as early as 2 months of age, but most patients undergo SCPA at 3–6 months. The SCPA cannot be performed earlier than 2–3 months of age because PVR is too high before this age, precluding sufficient PBF, systemic oxygenation, and systemic CO with the SCPA circulation. Reasons for “early” SCPA include increasing cyanosis from mBTS or RV–PA shunt narrowing, or need to address other surgical issues such as residual coarctation of the aorta. These “early” SCPA patients often have a difficult postoperative course because of their relatively high PVR. A few SCPA patients do not require neonatal palliation, and so the SCPA is their first surgical intervention (see earlier). The SCPA operation is done with CPB support in most institutions; however, it is possible to perform an isolated SCPA without any other cardiac procedures without CPB, with the aid of a temporary shunt from the SVC to the RA with partial heparinization. This technique is designed to prevent cerebrovenous hypertension and hypoxic–ischemic brain injury during the period when the SVC is occluded. Surgical technique for isolated SCPA involves institution of CPB with cannulae in the aorta, SVC, and RA; cross-clamping of the aorta is avoided unless there are additional intracardiac procedures planned, and mild hypothermia to 32–34°C is utilized. The mBTS or RV–PA shunt, if present, is occluded immediately after institution of CPB, and then divided and oversewn. The SVC is transected at its junction with the RA (with care not to injure the SA node), the RA oversewn, and the SVC anastomosed to the right PA (Figure 25.10). If pulmonary atresia does not already exist, either congenitally or as a result of incorporating the native pulmonary valve into the neonatal palliation to create a neo-aorta as with Norwood stage I palliation, the main PA is oversewn. The pulmonary valve leaflets are also sewn closed to prevent thrombus formation in the pulmonary valve sinuses, which can embolize retrograde into the single systemic ventricle. Some patients have what is termed a “pulsatile Glenn” shunt, which refers to the SCPA while intentionally leaving some ejection from the pulmonary ventricle through the PA. This both elevates the PA pressure and produces a pulse pressure. The reasons for this configuration are usually tricuspid stenosis or other form of mild RV hypoplasia, or Ebstein’s anomaly (see Chapter 23) in which the RV is deemed inadequate to receive all of the SVC and IVC flow combined. This operation is also termed a one-and-a-half-ventricle repair.

Additional surgical procedures are frequently necessary at the time of the SCPA. These may include patch augmentation of the PAs, atrial septectomy, correction of residual coarctation after Norwood stage I palliation, AV valve annuloplasty or other repair for regurgitation, or correction of other significant anatomic problems. In the case of the hybrid stage I palliation for HLHS (see earlier), the SCPA is accompanied by complex aortic reconstruction and atrial septectomy. Heterotaxy syndrome patients (see earlier) often have bilateral SVCs, and the left SVC is anastomosed to the left PA in this case. The heterotaxy patients may also require either revision or primary repair of anomalous pulmonary venous drainage at the time of the SCPA. Most often these additional procedures will require aortic cross-clamping. A thorough understanding of these additional surgical procedures and preoperative discussion of the intraoperative plan with the surgeon and perfusionist are crucially important to ensure the best outcomes.

An anatomic variation of the SCPA that occurs in patients with heterotaxy syndrome and interrupted IVC deserves mention. In these patients, the suprahepatic IVC is not present, and subdiaphragmatic systemic blood return occurs via collateral circulation that is reconstituted above the diaphragm, and enters the azygous or hemi-azygous circulation. The SCPA in these patients diverts the majority of all caval blood flow to the SCPA; and thus the physiology more closely approximates that after the Fontan operation. This operation has been termed the Kawashima procedure [77]. These patients usually require a Fontan-type intervention later, in order to direct hepatic venous blood into the pulmonary circulation. If this is not done, many of these patients develop pulmonary
arteriovenous fistulae with right-to-left intrapulmonary shunting that produce profound hypoxemia. This condition is thought to result from the lack of an as yet uncharacterized “hepatic factor” directly perfusing the pulmonary circulation [78].

Some institutions perform the “hemi-Fontan” operation in lieu of the standard SCPA. This variation constructs the upper portion of the lateral tunnel Fontan (see later) by anastomosing the SVC to the right PA, and the top of the RA to the underside of the PA confluence [72]. A cryopreserved homograft patch is used to augment the anastomosis to the left PA, and a piece of this homograft is used to create a “dam” in the upper RA to direct blood flow into the PAs. The reason for performing this operation instead of a standard SCPA is that some surgeons believe it makes the later lateral tunnel Fontan completion a much more straightforward operation. The drawback to the hemi-Fontan is that it is a longer and more complex surgery sometimes performed with DHCA, and the SA node may be injured.

The majority of SCPA patients will be undergoing repeat sternotomy; and thus have mediastinal adhesions and increased risk for bleeding and pre-CPB arrhythmias from the extensive electrocautery required in some cases. Appropriate precautions include administration of antifibrinolytic agents, large-bore IV access with blood products prepared for immediate administration, the application of external cardioversion/defibrillation pads to the patient, and preparation of the heparin dose and a primed CPB circuit.

**Preoperative assessment**

The conversion from a circulation based upon complete mixing and parallel perfusion of both the systemic and pulmonary vascular beds via an arterial shunt to a “series” circulation where PBF becomes a diversion of systemic venous return requires certain precautions. In essence, the flow of blood through the pulmonary circulation must be free of significant impediments in order that systemic venous pressure does not reach physiologically unacceptable levels. These potential impediments take three forms: elevated PVR, AV valve dysfunction, and diminished ventricular compliance. Elevated PVR encompasses two distinct mechanisms: the size of the major branches or the state of the arteriolar resistance vessels. In patients with HLHS, one must also confirm that no obstruction to flow exists at the remnant of the atrial septum. With the caveat that systemic venous pressures of 16 mmHg or less are generally tolerated without significant sequelae, while those of 20 mmHg and over are associated with a variety of morbidities, very small differences distinguish those who do well with the operation from those who have a poor outcome. Candidates for SCPA have in the past routinely undergone cardiac catheterization prior to surgery, but more recently, non-invasive methods of assessing the anatomy and physiology, such as cardiac MRI, have been successfully utilized in patients who do not require catheter-based interventions before surgery [79,80]. Knowledge of PVR, ventricular end-diastolic pressure, AV valve function, and any residual obstruction at the atrial septum remnant is desirable prior to surgical intervention. In addition, anatomic information about the PA architecture is obtained via contrast injection to evaluate for the presence of accessory venous communications between the superior venous drainage and the heart or IVC (e.g., left SVC to coronary sinus). Postoperatively, such vessels could serve as a mechanism by which upper body venous return is diverted to the heart without passing through the pulmonary circulation, thereby resulting in unanticipated levels of hypoxemia. These data can be used to estimate the SVC pressure on completion of SCPA. Recognizing that this formula requires several assumptions that render it an oversimplification, one can estimate the postoperative SVC pressure as follows:

\[
P_{\text{SVC}} = \left(\frac{(P_{\text{PA}} - P_{\text{PV}})(Q_{\text{PA}} : Q_{\text{SA}})}{Q_{\text{PB}} : Q_{\text{SB}}}\right) + P_{\text{LA}}
\]

where \(P_{\text{SVC}}\) and \(P_{\text{LA}}\) represent the pressure determinations in the SVC postoperatively and the LA, respectively; \(P_{\text{PA}}\) and \(P_{\text{PV}}\) are the preoperative pressures in the PA and vein, respectively; and \(Q_{\text{PB}} : Q_{\text{SB}}\) and \(Q_{\text{PA}} : Q_{\text{SA}}\) are the Qp:Qs ratios before and after SCPA, respectively.

In infants approximately 6 months of age, we estimate the proportion of venous return coming from the upper body to be roughly equal to that from the lower body, although SVC flow may comprise as much as 60–70% of the total venous return in some. In other words, \(Q_{\text{PB}} : Q_{\text{SB}}\) approximates 0.5–0.7.

For example, assuming the following hemodynamics are measured preoperatively:

\[
P_{\text{PA}} = 17, P_{\text{PV}} = 8, Q:\text{Qs} = 1.5, \text{and } P_{\text{LA}} = 8
\]

the \(P_{\text{SVC}}\) postoperatively is

\[
\left(\frac{(17-8)(0.5)}{1.5}\right) + 8 = 11 \text{ mmHg}
\]

Unfortunately, several of the assumptions limit this sort of calculation to the level of a crude estimate. \(P_{\text{PA}}\) is notoriously difficult to measure accurately when the only source of PBF is a systemic-to-pulmonary shunt. Catheters placed across the shunt probably alter PBF while they are present, while PV wedge pressures to estimate \(P_{\text{PV}}\) have a variety of limitations, particularly if PVR is elevated. The ventricular compliance is dynamic as well, particularly in the context of significant changes in ventricular volume and pressure loading conditions. In addition, the imposition of CPB and an ischemic interval have a negative impact on ventricular compliance, albeit a transient one if the operation proceeds according to plan. Finally, the Qp:Qs determinations depend upon PVR, which might be altered by the medications employed to sedate an infant for catheterization. Despite all the limitations, however, this estimate does help to predict problem patients as well as the type of problem.
they might encounter, whether related to PVR, ventricular compliance, or AV valve function.

Preoperative assessment should also incorporate an evaluation of other vital organ systems with a history of primary or secondary dysfunction. For patients receiving anticoagulant medications or functional platelet inhibitors, plans for the cessation of those therapies must be formalized. Very often these patients are taking low-dose aspirin with the goal of inhibiting platelet function to maintain mBTS patency; some institutions routinely discontinue aspirin 7–10 days preoperatively, while many do not. Careful history regarding the child’s response to sedative medications should also be elicited.

**Intraoperative management**

Infants typically return for SCPA between 3 and 6 months of age. Given their developmental stage and prior hospital experiences, some will manifest separation anxiety when taken from the parents. Thus, unless they have some contraindication, sedative premedication is administered orally prior to surgery. Although a variety of sedative potions are available, we prefer pentobarbital 4 mg/kg given orally because of its potency and duration of action. When administered 45–60 minutes in advance, a high proportion of patients will be sleeping. This serves to allay parental anxiety and also facilitates induction with a volatile inhaled anesthetic agent, if that is the planned technique.

Anesthesia can be induced with a variety of IV or inhaled agents. Unless the preoperative evaluation has revealed myocardial dysfunction or significant unusual hemodynamic loading conditions (e.g., arch obstruction, AV valve insufficiency), these infants generally tolerate nearly normal doses of anesthetic agents without manifesting untoward cardiovascular effects. We usually employ a combination of inhaled anesthetic, opioid, and muscle relaxant. Most commonly, the total opioid administered for the case is the equivalent of fentanyl 5–10 μg/kg, with the desired goal being sufficient emergence from the anesthetic effect to permit tracheal extubation on arrival to the cardiac ICU.

Although these infants at the time of anesthetic induction have the same anatomy and physiology as the newborn following stage I, subtle changes have occurred in the intervening months that make them significantly more resilient. Maturation and compensatory mechanisms in myocardial development render the heart more capable of managing the excess volume load of a parallel circulation. In addition, through differential growth, the shunt is more restrictive, protecting the infant from excessive acute volume loads irrespective of manipulations that lower PVR significantly. Finally, the baseline PVR is low, so even extreme measures cannot produce a substantial reduction in PVR from baseline values, and therefore any Qp:Qs change is comparably small. Nevertheless, we try to minimize any additional volume burden that might be placed on the ventricle prior to CPB and planned ischemia by minimizing supplemental oxygen delivery and ventilating to normocapnia.

All standard non-invasive monitors are applied for induction. An intra-arterial catheter is placed for continuous monitoring following tracheal intubation. The site selected for this catheter varies according to a variety of considerations related to congenital or acquired vascular anomalies. The placement of a BT shunt may have compromised the ipsilateral subclavian artery. In addition, previous monitoring and catheterization sites may not be available. There are also a variety of aortic arch branching patterns, some of which result in stenosis of the subclavian supply. Non-invasive arterial pressure measurement on all four extremities provides the data necessary to identify the appropriate site(s). Cannulation of the central veins via the jugular or subclavian is avoided in many institutions out of concern for the implications of thrombosis in those vessels. Others will cannulate the femoral vein as the major central venous access, and place a small (3 French) catheter in the right internal jugular vein for the purpose of monitoring PA pressure after surgery for 12–24 hours. This catheter is removed early in the postoperative period.

Unlike stage I, the SCPA provides significant hemodynamic benefit. With occlusion of the shunt, the circulations are no longer connected in parallel, thereby reducing the volume output demand for the RV to that necessary to perfuse the systemic circulation alone. PBF becomes a diversion for venous return from the RV to that necessary for the systemic circulation as the volume of blood flow to the upper body is at least as great as that to the lower body at 6 months of age, the mixture of oxygenated and deoxygenated blood remains 1:1 or higher. Thus, the expected systemic oxygen saturation tends to increase slightly, but the heart need only accomplish half the volume work (Qs) to accomplish this. Most patients exhibit robust hemodynamics on completion of this procedure. Although we usually infuse low-dose dopamine (1–3 μg/kg/min) via the atrial catheter, it may not be necessary in many patients. Infants exhibiting substantial diastolic dysfunction or valvar regurgitation may benefit from an inodilator such as milrinone. When anticipated on the basis of preoperative information, a loading dose may be administered during rewarming on CPB.

The strategy for managing PVR changes dramatically as well. With PBF no longer relying upon “passive” venous return (i.e., no pump to propel blood through the pulmonary circulation), measures designed to minimize the impediments to PBF assume paramount importance. As medical therapies are limited in their capacity to produce reliable, substantial improvement in ventricular compliance or AV valve function, attention is focused on minimizing PVR. Shortly before the termination of CPB, the tracheal tube should be cleared of secretions and the lungs completely re-expanded, as PVR will be minimized at normal FRC. Both atelectasis and alveolar overdistension increase PVR. A tidal volume designed to achieve a normal PaCO₂ at a respiratory rate no greater than 20 is selected. Doppler flow studies have demonstrated that
PBF occurs preferentially during the expiratory phase of positive pressure ventilation (PPV) in patients following cavopulmonary anastomosis, and thus we strive to limit rate and inspiratory time to no greater than 1 second [81,82]. Positive end-expiratory pressure (PEEP) is only applied judiciously to preserve normal FRC, based upon investigations in Fontan patients demonstrating significant reduction in cardiac index mediated by an increase in PVR at PEEP values over 6 mmHg [83]. Ventilatory strategies producing PaCO$_2$ of 45–50 mmHg will increase cerebral blood flow, thus increasing PBF through the direct SVC–PA connection. This strategy will not only increase systemic and cerebral oxygen saturation, but also increases systemic oxygen delivery [84,85]. In some instances of significant hypoxemia despite optimizing other measures, nitric oxide inhalation can be used to lower PVR. Some institutions routinely administer nitroglycerine via a catheter placed in the internal jugular vein (see earlier) with the thought that this will facilitate lower PVR; this practice has not been subjected to careful outcome studies.

Immediately following termination of CPB, MUF is instituted. MUF offers significant benefit to patients following cavopulmonary anastomosis [86]. Postoperative blood loss and the proportion of patients demonstrating significant pleural and pericardial effusions are both significantly reduced. Other investigators have shown benefits in pulmonary function across a wider spectrum of patients that may prove particularly crucial in this population.

Infants for SCPA represent a high-risk group for postoperative bleeding. They have several risk factors that tend to exacerbate bleeding, including age less than 2 years, reoperation, hypoxemia, frequent use of aspirin, and, in some, deep hypothermic bypass management. Upon completion of MUF, the heparin effect is rapidly reversed with protamine. Fresh whole blood, if available, comprises the preferred product for blood replacement following protamine administration. As described previously, this product provides restoration of all hemostatic elements, including platelets, and thereby limits donor exposures as well. In the vast majority, SCPA can be performed while limiting patient exposure to a single blood donor.

### Specific problems in the immediate postoperative period

Hypoxemia of greater magnitude than anticipated represents the most common postoperative problem encountered by patients following SCPA. In some instances, this may represent a manifestation of hypovolemia and diminished PBF, while in others it might reflect the mechanical ventilation strategy. In the latter circumstance, PaO$_2$ should rise as ventilatory support is tapered. In the absence of improvement with manipulation of intravascular volume or ventilation, diagnostic evaluation is indicated to search for connections that enable venous return from the upper body to bypass the pulmonary circulation and enter the heart or lower body venous system (e.g., to the coronary sinus). Often these collateral vessels can be occluded using transcatheter coil embolization, but the hemodynamic impact of occlusion should be tested with a balloon catheter prior to definitive embolization. The presence of a catheter in the SVC that measures PA pressure, in combination with an atrial pressure measurement, can give important information in the SCPA patient with hypoxemia.

Although the incidence of myocardial dysfunction is significantly lower following SCPA, it does occur. In the absence of significant hemodynamic causes (e.g., aortic arch obstruction, AV valve regurgitation), one must suspect an issue with myocardial protection or coronary perfusion. Despite their young age, some infants have developed extremely thick ventricular walls, particularly in the context of a high Qp:Qs and residual aortic arch obstruction. Adequate protection for these ventricles requires meticulous technique. Even under optimal circumstances, the compliance of these hearts may not return.

A very important physiological principle after SCPA is the creation of the "cavopulmonary–cerebral" circulation (Figure 25.11). This refers to the connection of the SVC, which drains the cerebral circulation, to the PA. Because of the relatively large size of the young infant’s brain, and responsiveness of cerebral blood flow to the PaCO$_2$, the PaCO$_2$ has an enhanced direct effect on PA flow after the SCPA. Higher PA flow means more oxygenated blood flowing through the lungs, resulting in higher arterial oxygen saturation, and also more blood return through the pulmonary veins to the LA, which in turn will increase the systemic CO of better oxygenated blood. A PaCO$_2$ of 40–45 mmHg results in improvements in cerebral and systemic oxygenation and systemic CO, compared with a PaCO$_2$ in the 30–35 mmHg range [84,85]. Therefore, in the setting of a lower PaO$_2$ (<35 mmHg) and SpO$_2$ (<75%) than desired, it is important to ensure appropriate PaCO$_2$ levels. If, despite these maneuvers, PVR is felt to be elevated, inhaled nitric oxide can be added. Among other benefits of earlier extubation of the trachea, the mild elevation in PaCO$_2$ with spontaneous ventilation has significant advantages for the cavopulmonary–cerebral circulation. In addition, elevating the head 30–45° immediately after completion of surgery, and maintaining a neutral position of the neck, without rotation, extension, or flexion, will promote optimal cerebrovenous drainage and improve oxygenation.

Another commonly observed problem early in the postoperative period after SCPA is systemic hypertension. One of the proposed mechanisms for this phenomenon is the readjustment of the cerebral circulation to higher venous pressures after the SCPA. Before SCPA, the cerebral venous pressure, as measured in the SVC, is usually 4–8 mmHg; after SCPA, SVC pressure is equal to PA pressure and is elevated to a mean of 12–18 mmHg. The cerebral perfusion pressure (CPP) is thus reduced and the hypertension is thought to be a response to preserve CPP. Table 25.4 presents hemodynamic and oxygenation
Chapter 25 Anesthesia for the Patient with a Single Ventricle

Cerebral circulation

Superior vena cava

Inferior vena cava

Systemic circulation

Pulmonary circulation

Systemic Ventricle

Figure 25.11 The cavopulmonary–cerebral circulation after superior cavopulmonary anastomosis. The relatively large brain of the young infant carries a large percentage of the cardiac output. Hyperventilation will decrease PaCO₂, constricting the cerebral arterioles and decreasing cerebral blood flow and cerebral oxygen saturation. This in turn decreases superior vena cava flow, decreasing pulmonary artery flow, which will lead to decreased systemic arterial oxygenation. (Source: Stephen A. Stayer, MD. Reproduced with permission.)

Table 25.4 Hemodynamic status and differential diagnosis in the postoperative superior cavopulmonary anastomosis patient

<table>
<thead>
<tr>
<th>Status</th>
<th>PAP (mmHg)</th>
<th>LAP (mmHg)</th>
<th>TPG (mmHg)</th>
<th>SpO₂ (%)</th>
<th>Etiologies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>10–15</td>
<td>2–6</td>
<td>&lt;10</td>
<td>80 ± 5</td>
<td>Ideal status</td>
</tr>
<tr>
<td>Elevated PAP</td>
<td>&gt;15</td>
<td>2–6</td>
<td>&gt;10</td>
<td>&lt;75</td>
<td>High PVR; PA or PV obstruction</td>
</tr>
<tr>
<td>Elevated LAP</td>
<td>&gt;15</td>
<td>&gt;8–10</td>
<td>&gt;10</td>
<td>&lt;75</td>
<td>Ventricular systolic/diastolic dysfunction; sub-AS; AVVR; tamponade</td>
</tr>
<tr>
<td>Cyanosis</td>
<td>10–15</td>
<td>2–6</td>
<td>&lt;10</td>
<td>&lt;75</td>
<td>Decreased CBF; PV desaturation; decompressing veins; hypovolemia; anemia</td>
</tr>
</tbody>
</table>

PAP, pulmonary artery pressure as measured in the superior vena cava; LAP, left or common atrial pressure; TPG, transpulmonary pressure gradient (PAP–LAP); PVR, pulmonary vascular resistance; PV, pulmonary vein; AS, aortic stenosis; AVVR, atrioventricular valve regurgitation; CBF, cerebral blood flow.

status problems and differential diagnosis in the early postoperative period after SCPA.

Outcomes

Outcomes following SCPA have been excellent in experienced centers, with operative survival over 96% [87–90]. While some infants who have had a Sano modification of stage I may require an earlier SCPA [91], this intervention can be performed at 3 months with no discernible difference in mortality, morbidity, or ultimate suitability for Fontan operation [90,91]. This observation has led some to advocate for earlier SCPA routinely as a means to reduce interstage mortality [92]. Attrition between the SCPA and Fontan completion for HLHS patients was reported recently by Carlo et al. [93]. Of 92 patients from the same institution who were 30 or more days after the SCPA and had been discharged from the hospital, eight died and three required transplant for an attrition rate of 12%. Interstage attrition was independently associated with moderate or severe tricuspid valve regurgitation and low weight at the time of the SCPA.
KEY POINTS: SUPERIOR CAVOPULMONARY ANASTOMOSIS

- SCPA is performed at 3–6 months of age and is normally the second stage of palliation in the Fontan pathway.
- SCPA results in significant unloading of the systemic ventricle and stabilization of the circulation, particularly in HLHS.
- Surgery is done with CPB but without aortic cross-clamping unless additional intracardiac surgery is required.
- The creation of a “cavopulmonary–cerebral” circulation with SCPA is an important concept; mild hypercarbia will promote cerebral and cavopulmonary blood flow and improve cerebral and systemic oxygenation and oxygen delivery.

Fontan completion

Surgical procedure

The basic surgical approach is illustrated in Figure 25.12. The two Fontan variations currently used are the lateral tunnel Fontan and the extracardiac Fontan. Earlier versions of the Fontan circulations used direct anastomosis of the RA appendage to the PAs, and have been abandoned due to long-term hemodynamic sequelae. These variations and conversion to standard modern Fontan configurations are discussed in Chapter 16.

In the lateral tunnel Fontan, CPB is instituted with aortobical cannulation, moderate hypothermia and aortic cross-clamping are utilized, and the RA opened. The underside of the right PA is anastomosed to the superior aspect of the opened RA, and an intra-atrial PTFE tunnel is created, connecting the opening of the IVC to the opening of the superior cavopulmonary connection [72]. Additional surgical procedures can be performed at the same time to correct defects, such as AV valve repair, PA patching and augmentation, atrial septectomy, and correction of residual coarctation of the aorta. A 3–5 mm fenestration may be created in the wall of the PTFE graft to allow right to left blood flow from the total cavopulmonary circuit to the common atrial chamber; this creates a “pop-off” effect to lower pressure in this circuit (Figure 25.13). The lateral tunnel configuration was the most common Fontan circuit through the 1990s and early 2000s, but with mid- and longer-term follow-up of these patients, several problems became evident. First, atrial arrhythmias are troublingly common 5–10 years after lateral tunnel Fontan, and the extensive intra-atrial suture lines were believed to become a nidus for these arrhythmias. Secondly, SVC and IVC blood flow streams collide directly in the atrial chamber and were thought to cause a loss of kinetic energy, thus reducing CO and leading to heart failure signs and symptoms. Finally, the frequently performed fenestration led to ongoing mild arterial oxygen desaturation and risk for systemic embolization of thrombi or air during medical or surgical interventions.

Because of these drawbacks of the lateral tunnel Fontan configuration, in recent years the extracardiac Fontan...
configuration has become the preferred surgery for most institutions. In this operation, which is performed with mildly hypothermic CPB and no aortic cross-clamping if no additional intracardiac surgery is required, an 18–20 mm PTFE tube graft is sewn outside the heart, connecting the IVC directly to the underside of the right PA. Some institutions report that the extracardiac Fontan can be performed with partial right heart bypass only [94], which reduces circuit volume and obviates the need for blood transfusion in many patients. The graft can be offset medially from the SVC–right PA anastomosis, so that IVC flow is preferentially directed to the left PA, and SVC flow to the right PA. The flowing streams of blood from SVC and IVC are believed not to lose as much kinetic energy in this configuration; this has been demonstrated using some ingenious fluid mechanics modeling derived from four-dimensional MRI studies in patients with the two types of Fontan circuit [72]. Although an attractive hypothesis, to date comparisons of power loss were not different in lateral tunnel vs. extracardiac Fontan connections; however, an undersized or stenosed Fontan connection was associated with power loss, emphasizing the importance of surgical technique and long-term thromboprophylaxis to maintain patency of the extracardiac conduit [95].

A potential drawback to the extracardiac conduit with offset SVC and IVC is that “hepatic factor” (see earlier) from the IVC may not perfuse the right PA, resulting in pulmonary arteriovenous malformations in the right lung. Several anecdotal cases have been observed at the Children’s Hospital of Philadelphia, necessitating some complex procedures to more evenly distribute the IVC flow to both lungs. A fenestration can be placed in the extracardiac configuration as well, but many surgeons prefer to avoid this, in order to avoid the need for future interventions to close the fenestration, arterial desaturation, and ongoing thromboembolic risks. A potential difficulty with the fenestration in the extracardiac conduit is that, if it needs to be enlarged or created, such as for treatment of protein-losing enteropathy (see later), this is considerably more difficult to perform in the catheterization laboratory than with the lateral tunnel Fontan.

The overall trend toward the extracardiac Fontan without fenestration at Texas Children’s Hospital is illustrated by a single-center experience from 2002 to 2008 of 226 Fontan operations [96]. In 2002, 87% of patients had a fenestration placed, with 93% undergoing lateral tunnel Fontan. By 2008, only 6% of Fontan patients had a fenestration placed, and 93% were extracardiac conduit. ICU stay and duration of intubation decreased during this period, although mean time of chest tube placement increased from 6.0 ± 3.5 to 6.6 ± 4.5 days (P = 0.025). On the other hand, at the Children’s Hospital of Philadelphia, in a report of 771 Fontan operations from 1992 to 2009, a fenestration was placed in 90% of patients, with this percentage increasing over the three surgical eras reported to 90.3% in 2003–2009 [97]. Extracardiac Fontan increased from 4.4% to 78.2% over the same eras. The issue of whether to fenestrate continues to be debated, with the fenestration conferring early postoperative benefits, such as shorter duration of chest tube drainage and hospital admission with the fenestration. This was demonstrated by Atz and Wessel in a long-term multicentered study of 536 Fontan patients, 67% of whom had a fenestration. Median hospital stay was 11 days with fenestration vs. 13.5 days without (P < 0.0001) [98]. In the longer term, patients with a fenestration were taking more cardiac medications and had lower resting SpO\textsubscript{2} (89% vs. 95%). Of those with a fenestration, 59% had been closed by later catheter intervention, 1% by surgical intervention; 40% closed spontaneously; and 19% remained open. The decision to create a fenestration is sometimes made on the basis of preoperative risk factors, such as HLHS, AV valve regurgitation, and high PVR. Although individual surgeons and institutions may differ, the overall trend in many institutions appears to be not to fenestrate, and to trade off a potentially longer early postoperative course, for lack of need for further catheter or surgical intervention, and to achieve normal SpO\textsubscript{2} early in the postoperative period.

In this manner, a total cavopulmonary connection is accomplished, separating the pulmonary and systemic
cirkulations, restoring normal physiologic blood flow patterns, eliminating or drastically reducing intracardiac mixing, and restoring normal or near normal arterial oxygen saturations. Because the newly created total cavopulmonary pathway does not have a pulmonary ventricle, blood flow into and through the pulmonary arteries is not aided by a pumping chamber. Instead, blood flow depends to a large degree on subatmospheric intrathoracic pressure promoting blood flow from the extrathoracic systemic venous system to the intrathoracic venous system. This flow also depends on a low PVR in the distal pulmonary vascular bed and on lack of any anatomic barriers, i.e., narrowed cavopulmonary anastomosis, branch PA stenosis, or pulmonary venous obstruction. Function of the systemic ventricle and lack of AV valve regurgitation are also important for the ideal Fontan connection; either one of these scenarios elevates end-diastolic and common atrial pressures, increasing resistance to flow across the pulmonary circulation. PPV will reduce flow into the cavopulmonary circuit, reduce PBF, pulmonary venous return to the systemic ventricle, and CO. From the time of closure of the sternum to tracheal extubation, the Fontan patient is at risk of lower CO with PPV, a risk that recurs for subsequent non-cardiac surgery and other interventions requiring PPV. The effect of PPV is overcome by increasing right-sided filling pressures, i.e. CVP, inotropic support, and, whenever possible, minimizing PEEP and allowing the patient to initiate their own ventilator breaths in the OR or ICU by utilizing a pressure- or volume-support mode of ventilation. This profound effect of PPV is a compelling reason to extubate the trachea and resume spontaneous ventilation as soon as possible after the Fontan surgery; extubation in the OR or shortly after ICU admission is strongly preferred by many institutions. To demonstrate the effectiveness of this practice, Morales et al. studied 112 Fontan patients at a single institution between 2002 and 2006, during a period when practice was changing toward a strategy of extubation in the OR [99]. During this period, the 34% of patients extubated in the OR were compared with the 66% not extubated in OR. The two cohorts were not different with regard to age, surgery time, and cardiac anatomy. In the first 12 postoperative hours, mean PA pressure and mean common atrial pressure were lower, and mean arterial pressure higher, in patients extubated in the OR (all \( P < 0.05 \)). Inotropic score was not different, and no patient extubated in the OR required reintubation. The mean time of chest tube drainage, ICU and hospital length of stay, and hospital charges were all reduced in the early extubation group.

There is one other significant physiological aspect of the Fontan circulation that it is important for the anestesiologist to understand. Patients with a fenestration will have a small right-to-left intracardiac shunt, and therefore some arterial desaturation. Normally with a fenestration \( \text{SpO}_2 \) is 88–95% in the early postoperative period; however, even without a fenestration, the coronary sinus, which carries 3–5% of the total CO, empties into the left atrial side of the Fontan circuit, producing a small degree of arterial desaturation. In addition, many Fontan patients have veno-venous collaterals to various degrees, and these vessels can produce arterial desaturation after the Fontan if they ultimately drain to the left atrial side of the Fontan. Finally, as noted earlier, some patients develop pulmonary AV malformations, which persist after the Fontan and usually recede over time.

Precise timing of the completion requires weighing several considerations, each of which is incompletely understood. At a minimum, the interval between the two stages of the Fontan must permit restoration of optimal ventricular compliance at the new end-diastolic dimension. In the absence of a diagnostic tool sensitive or specific enough to evaluate this process, many have arbitrarily established a minimal interval of 9–12 months. Despite its hemodynamic resilience, hemi-Fontan anatomy and physiology do pose risks that may provide compelling reasons not to extend this interval inordinately. These children are subject to the risk of paradoxical emboli returning via the IVC, as well as the consequences of hypoxemia, which accelerate with age. Diversion of the IVC blood away from the pulmonary circulation may predispose the child to development of pulmonary arteriovenous malformations.

**Preoperative assessment**

In preparation for Fontan operation, the same considerations apply as discussed for SCPA; however, the implications are more significant. Unlike the patient following SCPA, the Fontan operation leaves the child’s CO nearly totally dependent upon PBF. Whereas impediments to PBF following SCPA might result in lower systemic oxygenation, they produce low CO after Fontan operation. Clinical experience suggests that infants and young children are far more tolerant of hypoxemia than diminished CO.

Although candidates for Fontan operation have traditionally undergone cardiac catheterization preoperatively, an increasing number are now evaluated only via cardiac MRI studies [100,101]. In a study of 119 consecutive Fontan patients who did not require interventional catheterization intervention prior to surgery, Fogel et al. compared the quality of information achieved in patients receiving cardiac MRI alone (\( n = 410 \)), cardiac catheterization alone (\( n = 410 \)), or both cardiac MRI and catheterization (\( n = 37 \)). Diagnostic success was >95% in all three groups, and all early post-surgical outcomes were equivalent. Significant radiation exposure was avoided in the cardiac MR only patients. One can use the catheterization data gathered to predict systemic venous pressure following Fontan operation in much the same way as we described for SCPA. A fenestration is often created connecting systemic and pulmonary venous return, in order to ameliorate early postoperative morbidity and provide a pathway that sustains ventricular preload under conditions that might impede PBF [100,102]. Apart from coronary sinus return and flow crossing the fenestration created in the
ICV to PA pathway, all systemic venous return traverses the pulmonary circulation. Thus, one would estimate the Qp:Qs following fenestrated Fontan operation to reach 0.9 or higher. As an example, in a child catheterized in preparation for Fontan operation, the following determinations were made:

\[ Q_p : Q_s = 0.6, P_{PA} = 12, P_{LA} = 8 \]

Estimation of the systemic venous pressure (which should be equal to the PA pressure) would be calculated as:

\[ P_{SVC} = P_{IVC} = P_{PA} = \left( \frac{(12 - 8)(0.9)}{0.6} \right) + 8 = 14 \text{ mmHg} \]

An interval assessment should include both cardiac and non-cardiac problems and interventions. Knowledge regarding previous experiences with sedation and anesthesia exerts significant influence on management options. Finally, a plan should be devised in conjunction with the patient’s cardiologist for the perioperative management of any cardiac drugs, antiocoagulants, or other medical regimens.

**Intraoperative management**

Patients most commonly present for Fontan operation between 15 months and 3 years of age. At this developmental age, they will demonstrate significant separation anxiety. We prefer to alleviate their anxiety with either pentobarbital (4 mg/kg given orally, maximum dosage 120 mg) or midazolam (0.5 mg/kg given orally, maximum dosage 15 mg). The history of each child’s response to previous sedatives assumes importance in governing the decision as to which regimen to employ.

As with infants for SCPA, anesthesia for Fontan operation can be induced with a variety of IV or inhaled agents. Unless the preoperative evaluation has revealed myocardial dysfunction or significant unusual hemodynamic loading conditions (e.g., aortic arch obstruction, AV valve insufficiency), these infants generally tolerate the qualitative hemodynamic effects of anesthetic agents in a manner that is similar to normal children, although inhalation induction is slower due to the right-to-left shunting bypassing the lungs and delaying anesthetic uptake [103]. We usually employ a combination of inhaled anesthetic, opioid, and muscle relaxant, most commonly limiting the total opioid administered to the equivalent of fentanyl 10–15 μg/kg. Our goal is sufficient emergence from the anesthetic effect to permit tracheal extubation on arrival in the cardiac ICU, assuming that the child is normothermic, exhibits appropriate hemodynamics, and has no significant ongoing bleeding.

All standard non-invasive monitors are applied for induction. The considerations for invasive arterial monitoring site selection remain as described for the SCPA. Similarly, the philosophy regarding systemic venous pressure monitoring and postoperative transthoracic monitoring catheters in the PA and common atrium remains consistent. Some anesthesiologists prefer lower extremity peripheral IV access for the Fontan operation, because of the direct route from the IVC to the atrium. The rationale is that if significant bleeding is encountered during repeat sternotomy, intravascular volume infused via the SVC circulation must pass through the PAs and pulmonary veins before entering the atrium, and ventricular filling could thus be delayed or lost to the surgical field through the bleeding structure.

Some institutions have utilized epidural opioids administered by the caudal route as a means to facilitate early tracheal extubation and analgesia. Stuth et al. reported a prospective, randomized, double-blind study of caudal morphine, 100 μg/kg before incision, with caudal saline placebo in 64 patients undergoing SCPA or Fontan operation [104]. There was no difference in rate of extubation within 30 minutes of the end of surgery plus freedom from reintubation within 24 hours (81% caudal morphine vs. 84% caudal placebo). Time to first supplemental morphine for analgesia was longer with caudal morphine after Fontan, but not SCPA. The authors concluded that early extubation was feasible for most patients with or without caudal morphine.

The immediate benefits from the Fontan operation are limited to improved systemic oxygenation at the expense of higher IVC pressure. SVC/PA pressure also increases to some degree because of the completion of the total cavopulmonary circuit and the contribution of the increased IVC pressure and flow. Volume and pressure loading conditions for the single ventricle do not change in response to this procedure. Nevertheless, this relatively brief operation is well tolerated by the majority of children, particularly the intracardiac lateral tunnel technique. The details of immediate post-bypass management are identical to those following SCPA. Management includes meticulous ventilation designed to minimize PVR, low-dose inotropic support, MUF, and rapid restoration of hemostasis with protamine and fresh whole blood. As noted previously, PEEP is employed only as necessary to preserve normal FRC.

**Specific problems in the immediate postoperative period**

Unlike the manifestations of diminished PBF following SCPA anastomosis, in which reduction in systemic oxygen saturation occurs, the same phenomenon after Fontan operation will cause reduced CO. The signs of the latter tend to be far more insidious and ambiguous. These patients require the utmost vigilance to maintain adequate intravascular volume during the process of rewarming and blood loss in the early postoperative period. Conduit or baffle fenestration tends to ameliorate some of the early postoperative hemodynamic instability. When fenestrated, the IVC conduit allows some blood to shunt from the systemic venous to the pulmonary venous system, acting to preserve ventricular preload despite diminished PBF [100,102].
Hypoxemia usually indicates some communication from the systemic venous system to the atrium. A modest degree of hypoxemia frequently occurs related to flow through a planned fenestration and the coronary sinus, which normally enters the atrium on what is functionally the pulmonary venous side. Systemic oxygen saturation less than 85–90% suggests more flow across the fenestration than usual, extremely low mixed venous oxygen saturation, or an additional venous channel diverting blood around the pulmonary circulation. Alternatively, pulmonary arteriovenous malformations, such as those described following the Glenn operation, may account for the hypoxemia. Distinguishing these prospects may require cardiac catheterization.

Myocardial dysfunction typically follows the same differential described previously for SCPA. In the absence of a hemodynamic cause, one must conclude that it reflects inadequate myocardial preservation, coronary perfusion, or a metabolic process. In the absence of remediable causes (e.g., hypocalcemia), supportive measures represent the mainstay of therapy. Arrhythmias can arise immediately following Fontan operation. While heart block is uncommon, junctional rhythms occur in a quarter of the patients. If the escape rate is sufficiently low to have a deleterious impact on overall hemodynamics, epicardial atrial or AV pacing usually proves beneficial. In the current era, tachyarrhythmias are less common in the early postoperative period, but more likely to have a significantly negative hemodynamic impact when they occur. Doppler interrogations of PBF patterns suggest that flow is most brisk during diastole under normal circumstances [105], perhaps explaining the intolerance of tachyarrhythmias. Alternatively, unfavorable hemodynamics may serve to provoke tachyarrhythmias. Table 25.5 presents the differential diagnosis of low SpO₂ and blood pressure in the postoperative Fontan patient.

### Outcomes

As with SCPA, operative mortality following Fontan operation in the current era is less than 2% in experienced centers [87,90,106], and HLHS is no longer an independent predictor of adverse outcome following Fontan operation [107]. This trend toward decreasing operative mortality is borne out by a report of the Society of Thoracic Surgeons’ (STS) Congenital Heart Surgery Database, of 2,691 Fontan operations in 71 centers from 2005 to 2009[108]. The aggregate operative mortality before hospital discharge was 1.3%; with a 25th–75th percentile interquartile range of 0–1.5%. In another report from the same database of Fontan operations 2000–2009, the median age of Fontan by institution varied from 1.7 to 4.8 years, and median weight from 10.5 to 16.7 kg; these factors had no effect on operative mortality [109]. However, a weight-for-age of >2 standard deviations below the mean was associated with increased hospital mortality, early Fontan failure, and increased length of stay. Patients with heterotaxy syndrome undergoing the Fontan operation have higher operative hospital discharge mortality (4.2% with heterotaxy vs. 1.8% without heterotaxy) in another report from the STS database [110]. In a series from the Children’s Hospital of Philadelphia, 592 patients underwent primary Fontan from 1995 to 2009, and 11 (1.9%) had early Fontan failure, defined as death, need for ECMO, Fontan takedown to SCPA, or transplantation within 30 days [111]. Five of these patients (46%) died, as opposed to overall mortality of 0.8%. Longer CPB times, elevated end-diastolic pressure, extracardiac conduit, and not having a prior SCPA were all risk factors for early Fontan failure.

Significant morbidity and late mortality can occur following Fontan completion, including deteriorating ventricular function, arrhythmias, thrombotic events, and protein-losing enteropathy (PLE). In a cohort of 330 patients evaluated a median of 8 years following Fontan operation, the rates of freedom from death or transplant at 5 and 10 years were 95% and 93%, respectively. Overall parental assessment of their child’s health was excellent (57%) or good (38%), cardiac performance was New York

### Table 25.5 Hemodynamic status and differential diagnosis of abnormalities in the postoperative Fontan patient

<table>
<thead>
<tr>
<th>Status</th>
<th>PAP (mmHg)</th>
<th>LAP (mmHg)</th>
<th>TPG (mmHg)</th>
<th>Systolic BP (mmHg)</th>
<th>SpO₂</th>
<th>Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>10–15</td>
<td>2–6</td>
<td>&lt;10</td>
<td>85–95</td>
<td>95 ± 5</td>
<td>Ideal status</td>
</tr>
<tr>
<td>Decreased PAP</td>
<td>8–10</td>
<td>0–4</td>
<td>&lt;10</td>
<td>&lt;80</td>
<td>90 ± 5</td>
<td>Hypovolemia</td>
</tr>
<tr>
<td>and LAP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated PAP</td>
<td>&gt;15</td>
<td>2–6</td>
<td>&gt;10</td>
<td>80 ± 5</td>
<td>90 ± 5</td>
<td>High PVR; PA or PV obstruction</td>
</tr>
<tr>
<td>Elevated LAP</td>
<td>&gt;15</td>
<td>&gt;8–10</td>
<td>&lt;10</td>
<td>80 ± 5</td>
<td>90 ± 5</td>
<td>Ventricular systolic/diastolic dysfunction; AV dissociation; AVVR; tamponade</td>
</tr>
<tr>
<td>Cyanosis</td>
<td>10–15</td>
<td>2–6</td>
<td>&lt;10</td>
<td>85–95</td>
<td>&lt;85%</td>
<td>Excessive fenestration size or Fontan baffle leak; PV desaturation; decompressing veins; hypovolemia; anemia</td>
</tr>
</tbody>
</table>

PAP, pulmonary artery pressure as measured in the superior vena cava; LAP, left or common atrial pressure; TPG, transpulmonary pressure gradient (PAP–LAP); SpO₂, pulse oximeter saturation; PVR, pulmonary vascular resistance; PV, pulmonary vein; AS, aortic stenosis; AVVR, atrioventricular valve regurgitation.
Plastic bronchitis is a rare but serious and often life-threatening sequela after the Fontan operation [118]. This disease is characterized by proteinaceous casts in the tracheobronchial tree, resulting in chronic cough, wheezing, dyspnea, and hypoxemia (Figure 25.14). Progressive and severe airway obstruction may lead to death. The pathogenesis of plastic bronchitis is not completely elucidated, but elevated systemic venous and pulmonary artery pressures, and lower than normal CO are felt to contribute to a breakdown in airway mucosal integrity, injury to the alveolar–capillary interface, and leakage of cellular and proteinaceous material into the airway. Despite this theory, hemodynamic risk factors (e.g., elevated CVP and PA pressure, and low CO) are inconsistent in predicting this condition. Why a low percentage, i.e., <2–3% of Fontan patients, have this condition, while others with seemingly identical hemodynamic and anatomic status do not, is unclear. Avitabile et al. reviewed a series of 14 plastic bronchitis patients, and employed a tiered treatment strategy consisting of medical treatment with sildenafil and pulmonary toilet with bronchodilators, mucolytics, inhaled corticosteroids, and vest physiotherapy [118]. Thirteen out of 14 were treated with inhaled tissue plasminogen activator (tPA) two to four times daily. Nine underwent catheter interventions to correct hemodynamically significant recurrent or residual lesions, and three underwent cardiac transplantation. Follow-up ranged from 0.6 to 8.7 years. With this strategy seven out of 14 patients significantly improved, and seven out of 13 patients receiving tPA have been weaned off it; two out of three heart transplant patients are doing well.

Mid- and longer-term studies are conflicting as to the hypothesis that atrial arrhythmias are less frequent, and further interventions, such as need for permanent pacemaker or transplant for heart failure symptoms, are also less common with the extracardiac Fontan [119,120]. Lasa et al. [120] reported 193 patients undergoing either lateral tunnel \( n = 106, 55\% \) or extracardiac conduit \( n = 87, 45\% \) Fontan completion from 1995 to 2005. After an average of 7.1 years follow-up in the extracardiac conduit group vs. 10.5 years in the lateral tunnel group \( P = 0.0001 \), there was no difference in the overall incidence of late arrhythmias: 30% with the extracardiac conduit vs. 32% with the lateral tunnel \( P = 0.74 \). Pacemaker implantation was more frequent in the lateral tunnel group, at 11% vs. 2% \( P = 0.03 \). However, after adjustment for length of follow-up, there was no difference in the rate of pacemaker implantation \( P = 0.16 \) in the multivariable model. In a recent report of 529 patients who underwent extracardiac Fontan in Australia and New Zealand from 1997 to 2010, overall survival at 14 years was 96%, and rates of late adverse events were less for non-HLHS patients (3.3 per 100 patient-years with non-HLHS, vs. 7.9 per 100 patient-years with HLHS, \( P < 0.01 \)) [121]. Additional longer-term studies are needed to establish the whether the extracardiac conduit is superior with regard to incidence of arrhythmias or other adverse events; but it appears that contemporary surgical practice has already evolved ahead of these long-term data.

**KEY POINTS: FONTAN COMPLETION**

- The Fontan, or total cavopulmonary connection, is the final palliation for single-ventricle anatomy and is normally performed at 18 months to 3 years of age.
- The two common Fontan configurations are the lateral intra-atrial tunnel, and the extracardiac conduit; the extracardiac conduit is the one most commonly performed in recent years.
- A fenestration can be created to lower cavopulmonary pressure and improve systemic CO, at the
expensive of some arterial desaturation. Debate exists about fenestration; early postoperative course is often shorter and less complicated, but in the longer term the fenestration may require closure.

- PPV, hypovolemia, and loss of AV synchrony are all very detrimental to the Fontan circulation because of lack of a pulmonary ventricle; early extubation, maintenance of intravascular volume, and AV synchrony (sinus rhythm or AV pacing) are key goals of the Fontan operation.

Heart transplantation for single-ventricle malformations

Although cardiac transplantation has been performed in selected patients with single-ventricle malformations in late childhood and adolescence for progressive ventricular dysfunction, this strategy gained widespread notoriety when it was advocated for neonates with HLHS. In 1986 Bailey et al. described successful allotranplantation methods for HLHS [122]. The most recent International Society for Heart and Lung Transplantation data reveal approximately 500 pediatric heart transplants occurring yearly, with roughly one-quarter occurring in infants younger than 1 year [123]; unfortunately, however, in excess of 1,000 children are born with HLHS each year in the USA alone [124]. A multicenter study of the fate of infants awaiting cardiac transplantation demonstrated that, although the number of infants with unpalliated HLHS listed for cardiac transplantation continued to decrease each year, 25% of these patients died while awaiting transplantation despite the fact that their mean time to transplantation was 1.5 months, significantly less than other subgroups studied [125]. The group of patients awaiting transplantation will also continue to grow as children with HLHS who have failed surgical palliation are referred for cardiac replacement or “rescue transplantation” [120]. In a review of 417 infants and children transplanted at Loma Linda over 20 years, while over one-third of patients studied were primarily transplanted for HLHS, 9 patients had previously undergone surgical palliative procedures for HLHS [126]. Extending this therapy generally would likely result in an increase in both waiting time to transplantation and pre-transplant mortality, although increased utilization of hybrid procedures may allow more prolonged waiting periods in neonates with an increased margin of survival. Additionally, increasing experience and success with ABO-incompatible infant and pediatric cardiac transplantation may also assist in enlarging the list of potential donors for patients who require transplantation [126].

While 10-year survival rates of 76% have recently been reported in a cohort of patients who underwent cardiac transplantation as infants, concerns regarding both long-term survival and quality of life for recipients continue to persist. Of 31 survivors of infant cardiac replacement in one institution, three have undergone retransplantation, six have significant renal insufficiency, five have acquired post-transplant lymphoproliferative disease, and five have been diagnosed with coronary artery disease [126]. For the relatively small proportion of neonates with HLHS who are currently listed for transplantation, the waiting period can extend as long as 6 months and the mortality as high as 30% during that interval [125,127]. Consideration needs to be given to the long-term impact of the decision to pursue transplantation. Chronic immunosuppression and rejection limit 12-year survival to 55% in all pediatric heart recipients, and infants with congenital heart malformations fare even less well [128]. Beyond the initial year, mortality in pediatric transplant recipients is approximately 3% per year, whereas comparable mortality following Fontan operation is <1% per year [129,130].

A significant percentage of patients with HLHS experience long-term ventricular failure, and some are listed for orthotopic heart transplantation (OHT), even though the initial intention was to pursue the full Fontan palliation pathway. Murtuza et al. reported on 16 OHTs in HLHS patients from a single center from 2000 to 2011, and compared outcomes of these patients with 154 receiving OHT for cardiomyopathy, out of the total population of 209 OHT [131]. The 30-day survival was 100% in the HLHS group vs. 98.1% in the 154 patients transplanted for cardiomyopathy, and there were 1- and 5-year Kaplan–Meier survival rates of 100% for HLHS and 87.5% for the cardiomyopathy group (P = 0.393). The authors conclude that early and mid-term survival rates are good after OHT in HLHS patients, and that this should be a consideration early in HLHS patients with systemic ventricular failure. Cardiac transplantation is discussed in detail in Chapter 27.

Non-cardiac surgery and anesthesia for the patient with a single ventricle

Single-ventricle patients undergo multiple anesthetics and sedations for procedures other than cardiac surgery, including catheterization, MRI, CT, and vascular access procedures. Feeding difficulties are common after the neonatal palliation stage, and many of these patients require gastrostomy tube feeds. Many other non-cardiac anesthetics are required for a variety of procedures. If a procedure is elective, the period after the SCPA and before the Fontan completion confers a more stable circulation, free from the effects of cardiac volume load and delicate balance of PVR:SVR in the shunted single ventricle, and also avoiding the Fontan circulation with its deleterious effects of PPV and hypovolemia. Whenever possible, elective anesthetics should be scheduled for this period. Non-cardiac anesthetics for single-ventricle patients are discussed extensively in Chapter 30.
Summary

Single-ventricle lesions account for approximately 5% of CHD at birth [132]. However, these patients now undergo staged palliative reconstruction, and require multiple additional anesthetics for diagnostic procedures, cardiac catheterization, and non-cardiac surgery, and have a high rate of further intervention after the Fontan completion. Single-ventricle patients therefore comprise a larger proportion of the anesthetic population for the pediatric cardiac anesthesiologist in the modern era at major centers. At Texas Children’s Hospital, this proportion was 13.7% of anesthetics provided by the Division of Pediatric Cardiovascular Anesthesiology from 2010 to 2013 (data from the Congenital Cardiac Anesthesia Society/Society of Thoracic Surgeon’s Database provided by David Vener, MD). The anesthesia management for patients with a single ventricle encompasses a wide spectrum of care. Careful assessment and planning entail a comprehensive understanding of the typical physiology at each stage of the reconstructive sequence, the specific condition of each patient with respect to that physiology, and the impact that the proposed procedure is likely to have. Armed with that knowledge, an anesthesiologist can design a plan taking into account the qualitatively predictable effects of anesthetic agents, airway and ventilatory manipulations, and cardiovascular drugs. This plan is titrated to achieve the desired effects in each patient. No absolute formulas exist. Rather, absolute needs, expectations, capabilities, and goals vary between institutions, clinicians, and patients. Optimal results entail carefully orchestrated interactions among anesthesiologists, surgeons, cardiologists, and intensivists.

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http://www.wiley.com/go/andropoulos/congenitalheart


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CHAPTER 26

Anesthesia for Miscellaneous Cardiac Lesions

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Introduction

The congenital cardiac anesthesiologist is often faced with caring for patients with lesions and diseases that do not fit neatly into the anatomic and surgical classifications presented elsewhere in this book. This chapter presents vascular rings, coronary artery anomalies, pericardial effusion and tamponade, mitral regurgitation (MR), cardiac tumors, aortic aneurysm and aortopathy, and mediastinal masses. The anatomy, incidence, and natural history are reviewed for all lesions, followed by a discussion of pathophysiology. Surgical approach and outcomes are discussed next, and finally anesthetic considerations and approach are presented for each lesion.

Vascular rings

Classification, anatomy, and incidence

Vascular rings have a reported incidence between 1 in 1,000 births and 1 in 10,000 births [1,2]. The abnormalities develop from aberrations of the resorption of the six

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embryonic aortic arches that connect the primitive dorsal and ventral aorta. Normally, the left part of the fourth arch persists as the aortic arch. Persistence of the right part creates a right arch, while persistence of both parts of the fourth arch creates a double aortic arch. When these arch abnormalities form a ring, partial in some cases, they may produce either esophageal or tracheal compression or obstruction. Chapter 4 presents an extensive discussion of the embryology of congenital cardiac and vascular defects. The presence of a complete ring would appear to provide an anatomical explanation for obstruction of the encircled structures, but the relationship between symptoms and the ring and whether it is open or closed is complex and varies with the subgroups of lesions. A comprehensive classification of vascular rings is complex, as an extraordinary number of possible combinations of abnormalities are possible. The International Nomenclature and Database Conferences for Pediatric Cardiac Surgery [3] produced a pragmatic summary noting that describing the particular anatomy of the patient and planning for management based on that description (and symptoms) were more important than creating a “classification.” These authors noted that more than 95% of cases associated with symptoms could be described by four categories (Table 26.1):

1. Double aortic arch
2. Right arch/left ligamentum
3. Innominate artery compression of the trachea
4. Pulmonary artery sling.

It is notable that a variant of an otherwise normal left aortic arch is the presence of an aberrant right subclavian arising from the distal arch, which occurs in about 0.5% of normal individuals and is usually asymptomatic. This variant occurs in about a third of babies with trisomy 21.

### Diagnosis of vascular rings

Definitive diagnosis of vascular rings, once clinical suspicion has been aroused, relies on imaging and, in some cases, endoscopy. Historically barium swallow was a key investigation demonstrating the indentation of the ring on the esophagus. Magnetic resonance imaging (MRI) and computed tomographic (CT) angiography are now the modalities of choice, allowing three-dimensional (3D) reconstruction of the images and detailed surgical planning [4]. Assessment of the fibrous non-vascular parts of the ring is important. Echocardiography can contribute to the diagnosis but is dependent on achieving adequate echocardiographic windows, which may be difficult and is not suitable for assessing the airway [5]. Bronchography and bronchoscopy may be required to define the functional changes, particularly to assess tracheobronchomalacia and also to define the extent of tracheobronchial narrowing associated with a pulmonary artery sling.

### Vascular rings due to double and right aortic arches: anatomy and natural history

Double and right aortic arches are the result of persistence of the fourth right embryonic aortic arch and form complete rings around the esophagus and trachea [1] (Figure 26.1). They comprise less than 1% of congenital cardiac lesions. The double aortic arch group is commonly described according to whether the left or right arch is dominant or whether they are “balanced”, i.e., similar in size. The right aortic arch group may be subclassified by the origin of the left subclavian artery from the right arch. In one-third of right aortic arches, the right arch is a “mirror image” of the a normal left arch with the left subclavian a branch of the brachiocephalic first branch of the arch, whereas in two-thirds of cases, the left subclavian is the last major branch of the right arch, passing retro-esophageal to the left upper limb from the right side of the midline. This latter variant may also be associated with a dilatation of the origin of the vessel, reflecting a persistence of a segment of fetal aortic arch known as a Kommerell’s diverticulum. If this segment is not dealt with at the time of surgical repair, it can cause persistent or recurrent compressive symptoms. Double or right aortic arches with stenosis or coarctation of the aorta are rare. Patients with vascular rings should be echocardiographically assessed for associated cardiac anomalies that occur in approximately 10% of patients [6].

### Pathophysiology of vascular rings due to double or right aortic arches

Double and right aortic arches most commonly present in the first years of life with respiratory symptoms from

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**Table 26.1** Vascular ring operations at Children’s Memorial Hospital, Chicago, 1946–2009 (n = 412)

<table>
<thead>
<tr>
<th>Type</th>
<th>Subtype</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete vascular rings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Double aortic arch</td>
<td>Right arch dominant</td>
<td>139</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>Left arch dominant</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Balanced arch</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right aortic arch with</td>
<td>Retroesophageal left</td>
<td>140</td>
<td>34</td>
</tr>
<tr>
<td>left ligamentum arteriosum</td>
<td>subclavian artery</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mirror-image branching</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial vascular rings</td>
<td>Innominate artery compression</td>
<td>87</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pulmonary artery sling</td>
<td>40</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Left aortic arch, aberrant</td>
<td>6</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>right subclavian artery</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: Backer & Mavroudis [1]. Reproduced with permission of Wiley.
Figure 26.1 Embryonic aortic arches and double aortic arch. (A) Diagram of the embryonic aortic arches. Six pairs of aortic arches originally develop between the dorsal and ventral aorta. The first, second, and fifth arches regress. Preservation or deletion of different segments of the rudimentary arches results in a double aortic arch (B), a right aortic arch (C), or the “normal” left aortic arch (D). Ao, aorta; CCA, common carotid artery; L, left; PA, pulmonary artery; R, right; SA, subclavian artery. (Source: Backer & Mavroudis [1]. Reproduced with permission of Wiley.)

tracheal compression. These signs and symptoms include stridor, recurrent respiratory infections, a barking cough, and apnea in infants. Symptoms of esophageal obstruction are less common, being the primary presentation in about 15% of cases. Esophageal dysfunction may also interact with the respiratory symptoms, because reflux may lead to pulmonary aspiration and episodes of apnea. The development of aspiration pneumonia in the presence of tracheal dysfunction will increase the risk of prolonged pneumonia. The increased work of breathing associated with pneumonia will exaggerate the signs of airway obstruction that may have been absent or subtle when the patient was well. Vascular rings based on double and right aortic arches will encircle the esophagus and trachea. An in utero diagnosis by fetal ultrasound does not correlate with the timing and severity of symptoms, and surgery is not indicated unless the patient has symptoms. However, earlier surgical repair may limit or prevent the development of tracheomalacia, which is not immediately reversed by surgical relief of the obstruction due to the ring. The long-term outcome is generally very good. Most commonly these are isolated abnormalities, with approximately 10% of patients also having other significant cardiovascular anomalies.
Surgery for right and double aortic arch
Vascular rings are usually repaired through a left thoracotomy. Right thoracotomy or median sternotomy are occasionally used for unusual variants, with median sternotomy being most common when there are other cardiac lesions needing repair. The principle of the surgery is to ensure that the ring is completely divided, which may require division of the ligamentum arteriosum as well as a vascular structure or a fibrous remnant of a vascular structure [1, 7]. (Figures 26.2 and 26.3)

If a vascular structure is divided, such as one side of a double aortic arch, it is critical to ensure flow to all parts of the body is maintained. Test clamping and assessment of perfusion to the limbs and head may be required. Some variations of anatomy require reimplantation of blood supply. Such is the case with an aberrant origin of a left subclavian artery from a right aortic arch with a Kommerell’s diverticulum – a swelling at the insertion of the left subclavian. The Kommerell’s diverticulum can be resected and the left subclavian artery re-implantated onto the left common carotid artery [8] (Figure 26.4).

The outcome after surgical repair of vascular rings related to right or double aortic arches is very good with almost no mortality. Relief of obstruction is usually significant. Tracheomalacia may continue to produce postoperative symptoms, but these diminish with growth of the patient and tissue remodeling [9, 10]. Video-assisted thoracoscopic techniques may be used for these procedures and will influence the anesthetic management [11].

Anesthesia for division of vascular rings related to double or right aortic arches
The preoperative assessment should consider the impact the vascular abnormality has had on the patient, the details of the anatomy and function of the components of the vascular abnormality, the surgical plan, and the requirements for postoperative care. The severity of preoperative obstruction and chronic lung damage from

Figure 26.2 Double aortic arch division. (A) Double aortic arch, right arch dominant. (B) Dividing left aortic arch. (C) Arch divided. Ao, aorta; CA, carotid artery; L, left; LCCA, RCCA, left, right carotid artery; PA, pulmonary artery; R, right; SA, subclavian artery. (Source: Backer & Mavroudis [1]. Reproduced with permission of Wiley.)
recurrent infections is relevant to the risk of difficulty with oxygenation and ventilation during surgery and in the postoperative period. Chest radiograph findings suggesting chronic lung disease, tachypnea at rest, and rapid desaturation with crying are important indicators of associated lung disease. All other imaging studies, including CT scan, echocardiography, barium swallow, and MRI, should be thoroughly reviewed. The medical and surgical team should decide on optimal timing of surgical intervention, e.g., can the lung function be further optimized prior to surgery vs. the risk of delaying definitive therapy?

The anesthesiologist and surgeon must have a clear plan regarding the need for lung isolation, and discuss monitoring requirements if temporary or permanent occlusions of blood vessels are part of the surgical plan. This will influence whether intraoperative access to limbs for circulatory assessment by clinical means, pulse oximetry, intra-arterial pressure monitoring, transcranial Doppler or near-infrared spectroscopy (NIRS) will be required and whether a particular limb is most appropriate for arterial pressure monitoring (not at risk of being lost due to temporary clamping during the procedure).

Intra-arterial pressure monitoring is usually warranted due to the risk of massive hemorrhage, the need for significant intrathoracic retraction during the procedure and, in some cases, the need to confirm regional perfusion during intraoperative clamping of intrathoracic vessels. Central venous catheterization is usually done for these cases, especially if aortic clamping and suture lines will be required, as pharmacologic control of blood pressure is more safely performed with central venous access. Substantial peripheral venous access should be secured in anticipation of the possible need for rapid resuscitation in the face of surgical blood loss. The procedures usually are associated with minimal blood loss, but preparation should be made for the possibility of massive transfusion.

The tracheal narrowing from vascular rings will not usually prevent an endotracheal tube from being passed through the narrowing. It is rare that positive pressure ventilation and continuous positive airway pressure (CPAP) or positive end-expiratory pressure (PEEP) will not be sufficient to allow ventilation during induction of anesthesia. A single-lumen endotracheal tube is usually adequate for open thoracotomy and often acceptable for thoracoscopic procedures where lung retraction provides good surgical access. If desired, lung isolation may be achieved (see Chapter 19 for a discussion of lung isolation techniques). Rigid or flexible bronchoscopy may be performed pre- and post-procedure in some cases.

Most patients will tolerate early extubation if appropriate analgesia is provided. This will vary with the institution and whether an open or thoracoscopic technique was used. Thoracic epidural analgesia is used in some institutions for thoracotomy for vascular rings. Significant preoperative lung disease or predicted postoperative airway obstruction may require more prolonged intubation and respiratory support.

**KEY POINTS: VASCULAR RINGS BASED ON RIGHT OR DOUBLE AORTIC ARCH**

- It is important to assess the degree of airway obstruction and whether there is chronic lung disease.
- Confirm surgical approach (mostly left thoracotomy) and whether regional perfusion (limbs and brain) will need to be assessed intraoperatively (monitoring and arterial line placement).
- Plan postoperative management: early vs. late extubation.
- The tracheomalacia associated with most vascular rings is not immediately cured by relief of the vascular ring.
Innominate artery compression of the trachea: anatomy and natural history

Innominate artery compression of the trachea is not a true vascular ring [1] (Figure 26.5). Some degree of innominate artery indentation is normal in the first years of life, and the origin of the vessel from the aorta to the left of the trachea is also normal in young children. The normal changes in geometry of this region with growth cause the origin of the innominate artery from the aorta to move to the right of the trachea (not crossing it) and to rotate to the cranial side of the aorta. These changes decrease the degree of tracheal compression caused by the innominate artery as a child grows. Tracheal compression is more likely if the origin of the innominate artery from the aorta is more distal (to the left) and posterior than usual, resulting in anterior compression of the trachea as the vessel passes towards the right side across the front of the trachea. Severity of symptoms and efficacy of medical therapy for
Acute exacerbations associated with respiratory infection will influence the decision about whether to offer surgery or continue observation and medical therapy, knowing that the natural history of the condition is to improve with growth. Some other congenital abnormalities of this region, including congenital heart disease (CHD), and some patients with repaired esophageal atresia and tracheoesophageal fistula may cause “crowding” of the area, making innominate artery compression of the trachea more likely and perhaps less likely to resolve with time.

**Pathophysiology of innominate artery compression of the trachea**

Symptomatic innominate artery compression syndrome produces a localized narrowing of the trachea, often with a localized segment of tracheomalacia. Symptoms typically do not appear until there is more than 50% obstruction of the trachea. The condition presents with stridor and airway obstruction, often with an abnormal harsh cough relating to the associated tracheomalacia. Innominate artery compression of the trachea may underlie some presentations of recurrent croup. Because there is some degree of tracheal impression from the innominate artery in normal young children, it is important to not overdiagnose this condition with the risk of significant surgical intervention offered inappropriately.

**Surgery for innominate artery compression of the trachea**

Surgery for this condition is not commonly indicated except for significantly symptomatic patients where conservative therapy is deemed inappropriate. Most of the procedures are done through a left thoracotomy, but sternotomy and right thoracotomy have been used for vascular suspension procedures. Surgery can involve aortopexy of the innominate artery and aorta anterior to the sternum, which has a modest risk of recurrence, or reimplantation of the innominate artery so that its origin from the aorta is to the right of the trachea and from the cephalad aspect of the aorta [1] (Figure 26.6). This is a more complex procedure with a greater risk of complications, but definitively eliminates the innominate artery as a cause of tracheal compression. With either procedure, residual tracheomalacia may cause ongoing symptoms.

**Anesthesia for repair of innominate artery compression of the trachea**

The preoperative general assessment is similar to that described for vascular rings. The conduct of anesthesia is simplified if aortopexy of the innominate/aorta is the surgical technique, because the risk of major intraoperative complications or the need for vascular clamping is minimal. Reimplantation of the innominate artery will involve more specific and intense intraoperative monitoring, which will include consideration of the aortic surgery and temporary occlusion of the innominate artery. For continuous arterial pressure monitoring, an arterial
line can be placed in the left radial artery. Information about adequacy of collateral perfusion during clamping of the innominate can be gained by placing an arterial line in the right radial artery. Previous case series have not noted stroke as a significant risk during temporary clamping of the innominate artery, but monitoring of cerebral perfusion, e.g., with NIRS, may be warranted to confirm minimal risk of ischemic stroke due to poor perfusion relating to clamping. Anticoagulation (normally 100 units/kg heparin; target activated clotting time 180–200 seconds) is used to minimize the risk of embolus or thrombosis related to innominate artery reimplantation. Bronchoscopy, either rigid or flexible, is frequently performed pre- and post-procedure to assess results of surgery. Postoperative care will be predicated on similar principles to vascular ring procedures.

KEY POINTS: INNOMINATE ARTERY COMPRESSION SYNDROME

- Some innominate artery compression of the trachea is normal.
- Natural history is for obstruction to decrease with growth, so conservative management is often justified.
- Simple suspension aortopexy is usually adequate for cases that require surgery and will “buy time” for growth.
- Formal reimplantation of the innominate artery is more definitive surgery but far more complex a procedure with a number of potential complications.

Pulmonary artery sling with tracheal stenosis: anatomy and natural history

Pulmonary artery sling results from an aberrant course of the left pulmonary artery around the trachea, which may restrict the space in which the trachea forms [1] (Figure 26.7). The left pulmonary artery arises from the posterior surface of the right pulmonary artery and passes over the superior surface of the right main bronchus then posterior to the trachea and anterior to the esophagus to the left lung. The most important factor that determines prognosis is the association of this lesion with segmental narrowing of the trachea, and sometimes bronchi, with complete cartilaginous rings in the affected segment, the so-called “rat-tail trachea.” A long segment of narrowing worsens the prognosis. Curiously, these patients frequently do not present for some months after birth, often with airway obstruction associated with an apparently minor respiratory infection. Recent advances in tracheal reconstruction have been associated with improved outcome. Imaging studies are crucial for accurate diagnosis. Echocardiography may provide initial diagnosis, but anatomic detail is better provided by CT or MRI; cardiac catheterization is rarely indicated for this problem.

Pulmonary artery sling with tracheal stenosis: pathophysiology

Pulmonary artery sling pathophysiology is focused on the severity and length of the associated tracheobronchial narrowing. It is not clear whether the usual delay in presentation until some months of life represents primarily a failure of further growth of airway diameter or an increase in ventilatory requirements as the child grows. A common clinical scenario is an apparently minor respiratory infection in the middle of the first year of life, leading to obvious signs of increased work of breathing relating to respiratory obstruction with slow or incomplete resolution of the illness. Distinguishing this from the far more common bronchiolitis and laryngotracheobronchitis infections in children with underlying normal airways is difficult at the primary presentation. The severity of obstruction, failure of resolution, and recurrent presentation are the usual triggers for further investigation and diagnosis of the patient with pulmonary artery sling.

Surgery for pulmonary artery sling with tracheal narrowing

The long-term outcome of the surgical intervention for these patients depends on the tracheal reconstruction. The surgery is done through a sternotomy, on cardiopulmonary bypass (CPB). The aberrant left pulmonary artery can be dealt with at the time of reconstruction of the trachea, most commonly by dividing it and reimplanting it, to mimic the normal takeoff from the main pulmonary artery, but alternative methods to relocate the vessel in relation to the reconstructed trachea have been used.

For patients with a short segment of tracheal stenosis, resection of the stenosis, mobilization of the trachea, and direct anastomosis may be sufficient and relatively
straightforward surgery [1] (Figure 26.8). For patients with a longer segment of narrow trachea with complete rings, the long-term problem with tracheal reconstruction has been to achieve both continuing adequate airway patency and a functional tracheal epithelium. The airway patency must be throughout the respiratory cycle, which requires a degree of rigidity to resist collapse in expiration. For long segment reconstruction, the slide tracheoplasty has become the preferred surgical approach. Alternatives, such as simple patches (e.g., with pericardium), will usually be associated with tracheomalacia in the long term. Scarring and granulation formation and lack of ciliary function will often complicate stented patches, whether stented by external, surgically placed cartilage grafts or internal stents, similar to those used for vascular stenting. Alternative sources of tissue, such as laboratory-based tissue engineering or donor tissue, are possible, but slide tracheoplasty has the potential to provide airway patency,
with a non-collapsing wall and normal respiratory epithelial mucosa.

Slide tracheoplasty is a solution for many longer segment narrowings which optimizes use of native tissues to reconstruct the trachea and potentially proximal bronchi [12] (Figure 26.9). The technique involves an oblique division of the trachea, with the distal and proximal ends of the incision continued on the proximal trachea and distally, and potentially along a bronchus if there is bronchial involvement. The trachea is mobilized so that the oblique end of the proximal trachea can slide into the apex of the distal incision, and the oblique end of the distal trachea can slide into the apex of the proximal incision. This achieves expansion of the lumen, with essentially normal tracheal

Figure 26.9 Slide tracheoplasty. (A) The trachea is transected in the midportion of the tracheal stenosis. This site is determined by either external examination or internal bronchoscopic findings. The inferior portion of the trachea is incised anteriorly and the superior portion of the trachea is incised posteriorly. (B) The ends of the trachea are beveled as shown in the small inset. The suture line is started superiorly (parachute technique) and finished inferiorly just above the carina. (C) Completed slide tracheoplasty. (Source: Backer et al., 2000 [12]. Reproduced with permission of Elsevier.)
surgical management of vascular rings

1. Implant left PA into main PA anterior to the trachea
2. Left thoracotomy (muscle-sparing — fourth interspace)
3. Leave pleura open
4. Postoperative bronchoscopy
5. Divide lesser of two arches at insertion with descending aorta
6. Leave pleura open
7. Slide tracheoplasty for associated tracheal rings
8. Resect Kommerell’s diverticulum (if present) and transfer left
9. Suspend innominate artery to posterior sternum
10. Resect right lobe of thymus
11. Right anterolateral thoracotomy (third interspace)
12. Ligate/divide left pulmonary artery (PA)
13. Median sternotomy/extracorporeal circulation
14. Preserve blood flow to carotid/radial arteries
15. Ligate and divide ligamentum arteriosum
16. Leave pleura open

Anesthesia for repair of pulmonary artery sling and tracheal stenosis

The anesthesia assessment of these patients is particularly focused on the impact and extent of the associated tracheal stenosis. The indications and timing of surgery are entirely driven by symptoms related to the tracheal obstruction. The spectrum of these patients’ condition may well range from a minimally symptomatic child who is requiring no current intervention to a patient in a perilous situation with maximum intensive care support, with complex ventilator requirements and potentially requiring extracorporeal oxygenation or carbon dioxide clearance. Positive pressure ventilation in these patients is difficult to optimize and assessing flow volume loops created by different ventilator strategies can be helpful. Common strategies include permissive hypercapnea, attention to adequate expiratory time to minimize hyperinflation, which limits ventilation, and continuous positive pressure to maintain airway patency.

Anesthesia is as for other procedures requiring CPB. Passing an endotracheal tube through the larynx is initially as for a normal patient. The difference is that a tube that is appropriate for the upper trachea will not pass through the narrow segment. No attempt should be made to advance the endotracheal tube through the narrowing. Bronchoscopic assistance may be utilized or the tube can be gently advanced through the larynx until resistance is felt and minimally withdrawn from that point. The narrow segment of the trachea can easily be blocked by blood, swelling, or secretions associated with trauma to the mucosa, with potentially catastrophic results. Avoiding these complications by minimizing airway trauma is a primary aim. If required, suctioning may require a fine catheter and lubrication to clear secretions from the narrow segment. Suctioning may be necessary for adequate ventilation but runs the risk of traumatizing the mucosa. Suctioning may be life-saving if secretions or blood occlude the narrow segment. High inspiratory pressures may be required to inflate the lungs, as the narrow segment may have a very high resistance to flow. For this reason, consideration should be given to ensuring that the largest appropriate tube is placed above the narrowing to minimize the risk of excessive leak at high ventilator pressures or inability to generate adequate pressure. If there is sufficient length of trachea above the narrowing, a tube with a cuff, particularly one with the minimum
**Anomalous pulmonary origins of the coronary arteries**

There is wide anatomic variation of the coronary arteries. There are a number of common variants which are accepted as normal but which may have significance if disease of the coronary develops (e.g., proximal atheroma in a single coronary artery which gives rise to left and right coronary arteries) or surgery of the region is required (where intramural or unusually placed vessels may be more likely to be injured). The physiological function of the coronary arteries and the heart is usually normal in these variations.

The focus of this section is congenital anomalies of the coronary arteries. Acquired abnormalities are also important in childhood. These include infective causes, of which Kawasaki disease is the most prominent, iatrogenic causes arising from surgery or invasive cardiological procedures, and the development of abnormalities in relation to other lesions, such as the coronary perfusion issues that can be associated with supravalvular aortic stenosis.

The Congenital Heart Surgery Nomenclature and Database Project provided an excellent classification and review of the significance of anomalies of the coronary arteries [13]. The major types of coronary anomaly were divided into the following seven groups:

1. Anomalous pulmonary origins of the coronary arteries
2. Anomalous aortic origins of the coronary arteries
3. Congenital atresia of the left main coronary artery
4. Coronary arteriovenous fistulas
5. Coronary artery bridging
6. Coronary artery aneurysms
7. Coronary stenosis.

Supravalvular aortic stenosis is associated with sudden death, sometimes in association with apparently stable anesthesia, and the complex mechanisms, which may be both structural and dynamic, for the development of abnormalities of coronary perfusion in this condition are briefly discussed.

**Pathophysiology of ALCAPA**

The pathophysiology of ALCAPA is complex and will vary with the exact anatomy and the changing physiological circumstances as the neonate develops and pulmonary vascular resistance (PVR) and pressure falls. The ALCAPA vessel provides a connection between the pulmonary artery and the myocardium supplied by the left coronary artery. Left ventricular coronary perfusion is dependent on diastolic perfusion, as the pressure generated by left ventricular contraction prevents coronary perfusion during systole. In the early neonatal period, PVR and pulmonary artery pressure are high, compared with later in life. In this phase, the left ventricle may have adequate oxygenation, albeit with mixed venous blood with relatively low hemoglobin oxygen saturation, which can be adequate for left ventricular function. As PVR and pulmonary artery pressure decrease, flow in the ALCAPA vessel may reverse, acting as a fistula and causing run-off of coronary blood flow to the pulmonary artery, creating a “coronary artery steal” and worsening left ventricular perfusion. This will cause ventricular ischemia, which will lead to ventricular dysfunction, especially in diastole, which will lead to an increase in left ventricular diastolic pressures, thus further decreasing the perfusion pressure. The “coronary steal” may also effect right ventricular perfusion in both systole and diastole, if there are significant collaterals, but the presence of some systolic perfusion of the right ventricle muscle, as in normal coronary physiology, is protective. A peculiar potential benefit of the reverse flow in the ALCAPA vessel (towards the pulmonary origin) is that this may help to maintain PVR and pressure, potentially delaying the onset of symptoms.

The worsening left ventricular function will be associated with dilation of the left ventricle. Left heart dilation may be associated with a shift of the interventricular septum towards the right, with associated impairment of right heart function. Mitral valve regurgitation can be induced by both dilation of the left atrioventricular ring and ischemic dysfunction of the papillary muscles. This will lead to volume loading and further deterioration of left ventricular function with worsening pulmonary congestion and a low output state. The commonest
presentation of ALCAPA is at weeks to sometimes months after birth with a condition that is essentially a severe dilated cardiomyopathy of ischemic origin. All infants presenting with dilated cardiomyopathy must be closely screened for anomalies of coronary origin.

Variations in the anatomy of the ALCAPA may influence the presentation. As with normal coronary arteries, there may be significant differences in the balance of these arteries. The more that the right coronary is dominant, supplying significant portions of the ventricular septum and other regions of the left ventricle, the more likely it is that there will be later presentation with less severe deterioration in myocardial function. Similarly, stenosis of the ALCAPA vessel, which may occur at its origin, will actually lessen the impact of the coronary steal and allow more chance for collateral vessels from the right coronary to perfuse the left side of the heart. There is some evidence that these more delayed presentations may have a long-term negative impact, as the underlying ischemia will have been more long-lasting, producing fibrosis, and ventricular recovery after repair will be impaired. For patients with a dominant ALCAPA distribution, presentation is likely to be early with severe myocardial dysfunction. Although recovery in this circumstance can be excellent, some patients may have completed infarction of regions of the left ventricle with no prospect of recovery of function with reperfusion, and with a risk of formation of aneurysm of the left ventricle. The more severe early presentations are also at risk of lethal complications before surgical repair can be performed.

**Surgery for ALCAPA**

Historically, simple ligation of the ALCAPA vessel was used, improving survival [17]. This would prevent the coronary steal and, depending on the adequacy of collateral circulation, improve perfusion of the left ventricle. Mortality was still high and recovery of left ventricular function usually incomplete. This procedure is no longer performed in major congenital cardiac surgery centers. Current surgical management involves restoring aortic perfusion of the ALCAPA vessel, thus providing a two-coronary circulation originating from the aorta, usually by mobilization and reimplantation of the ALCAPA vessel onto the aorta [18–20] (Figure 26.10). A specific example that can be used for a very short ALCAPA vessel is the Takeuchi procedure. This involves using an intra-arterial pulmonary baffle to direct flow from a surgically created aortopulmonary window to supply the origin of the ALCAPA vessel with systemic arterial blood in situ, with patch expansion of the pulmonary artery to allow space for the baffle and prevent pulmonary obstruction [21–23] (Figure 26.11).

The unit managing these cases should be able to provide extracorporeal circulatory support with ventricular assist device (VAD) or extracorporeal membrane oxygenation (ECMO) if required. The techniques may be necessary as part of preoperative resuscitation or for support of the patient in the early postoperative period, as recovery of myocardial function is usually not immediate [24].

Imamura et al. reported a series of 26 ALCAPA operations over a 20-year period [25]. Twenty-one did not require ECMO support and five required ECMO for a mean of 10.7 ± 6.7 days. One patient in each group required cardiac transplantation, and four others required six reoperations (five for MR). There were no deaths in the series, and actuarial freedom from transplantation or reoperation at 5 years was 0% in the ECMO group, and 92% in the non-ECMO group. Chapter 32 presents a detailed discussion of mechanical support of the circulation.

There is controversy about the role of surgical procedures to improve mitral valve regurgitation at the primary operation, because mitral valve function usually improves as improved myocardial function results in decreased end-diastolic volume and better papillary muscle function [26]. In a recent series of 25 operations for ALCAPA, Kudumula et al. repaired the mitral valve only for moderate to severe MR, accompanied by structural mitral valve abnormalities, observed in four patients [27]. Two patients had mitral valve cleft, one had prolapse, and one had a dysplastic double orifice mitral valve. The one patient with a structural mitral valve abnormality that was not repaired at the original operation developed severe MR and required repair at a second operation. Of 14 patients in the series without structural mitral valve problems with moderate or severe MR, 13/14 had none or mild MR at the time of follow-up. Some surgeons still argue that there is a reasonable argument that surgical techniques that decrease the mitral valve annulus size but allow for future growth may improve mitral valve function acutely,
improving the performance of the dysfunctional early postoperative heart.

Anesthetic considerations for ALCAPA

The degree of myocardial dysfunction is the factor that dominates the condition and prognosis of these patients throughout the perioperative period. Preoperatively, the patient with ALCAPA may be receiving cardiorespiratory support, ranging from none to an intubated ventilated patient on ECMO. In between these extremes will be patients with various degrees of inotropic support receiving tailored vasodilators or, in some cases, vasoconstrictors. The general principle that a failing heart, especially with MR, will have output improved by systemic vasodilation is sound, but the severity of the dysfunction in some of these patients means there may be a role for vasoconstrictors. If the patient is already hypotensive, it is possible that the vasodilation is actually excessive for that heart and results in greater tachycardia. The poor coronary perfusion is worsened by both the systemic hypotension and the tachycardia. In this scenario of myocardial dysfunction with relatively excessive vasodilation, judicious use of vasoconstrictors may improve blood pressure and decrease heart rate, improving coronary perfusion while maintaining an acceptable cardiac output. The patient should be monitored for signs of inability of the heart to cope with the increased afterload or worsening MR.

Preoperative assessment of patients with ALCAPA should also include assessment of the complications of the myocardial dysfunction, such as respiratory, renal and hepatic dysfunction, as well as a general medical review.

The group of patients with ALCAPA who provide perhaps the greatest challenge for the anesthesiologist comprises those who have been diagnosed after presenting with respiratory distress, but who are stable and not requiring acute cardiorespiratory support. They may have intravenous access, and non-invasive monitors have been used. Echocardiography will have confirmed the diagnosis and the critically poor myocardial function. The anesthesiologist will be responsible for induction of anesthesia and stabilization of the patient prior to the initiation of CPB in a situation where minor changes in sympathetic drive or myocardial function might be associated with cardiac arrest. Induction of anesthesia, intubation, positive pressure ventilation, placing a central venous catheter or transesophageal echocardiography (TEE) probe, excessive anesthesia with myocardial depression or depression of central nervous system-driven sympathetic activity, or
inadequate anesthesia resulting in excessive sympathetic response can lead to life-threatening incidents. The anesthesiologist should be prepared to heparinize and defibrillate the patient at any time. The nursing, perfusion, and surgical team should all be prepared for the potential need for emergent sternotomy and initiation of CPB, and they should be in the operating room during the induction of anesthesia. If it is possible to obtain pre-induction arterial access without upsetting the patient, this is highly desirable for the earliest warning of cardiovascular compromise. This can sometimes be accomplished in young infants with local anesthesia, either topically or by injection, along with 50% N\textsubscript{2}O inhalation or small analgesic doses of fentanyl or other opioid intravenously.

The induction of anesthesia in patients with ALCAPA requires great care in slow titration of small increments of whatever drugs are selected to minimize the myocardial depression and vasodilation that accompanies usual doses of most of these drugs. Opioids, such as fentanyl and remifentanil, although tending to spare myocardial function, can rapidly depress central sympathetic drive, causing relative bradycardia and vasodilation, which may be poorly tolerated by these patients. Similar problems can arise even with drugs, such as etomidate and ketamine, that tend to preserve sympathetic function and cardiovascular stability in normal patients. Ketamine is a direct myocardial depressant and these hemodynamic effects are most commonly seen in the patient who has depletion of endogenous catecholamines, such as the infant with ALCAPA. Ketamine is also implicated as possibly inducing brain injury in the developing brain and some anesthesiologists avoid it in this age group. The complex risk balance of choice of agent and combination of agents for ALCAPA patients makes judicious, cautious use of agents with which the anesthetist is very familiar a reasonable choice.

Preoperative fluid restriction to manage pulmonary congestion may make the patient especially prone to hypotension with the initiation of positive pressure ventilation. Judicious intravascular volume loading at this time may prevent this. Successful transition to anesthesia and positive pressure ventilation may improve lung function and create some afterload reduction, which may improve left ventricular function. Lung compliance is usually low due to pulmonary congestion, and significant ventilator pressures are commonly required.

Maintenance of elevated PVR will minimize the “coronary steal” due to the ALCAPA flow into the pulmonary artery. Avoiding a high inspired oxygen concentration and maintaining a normal or moderately high arterial carbon dioxide level are key strategies for maintaining PVR, but pulmonary congestion secondary to left heart failure may mean that increased inspired oxygen levels and high ventilator pressures will be required. Significant positive end-expiratory pressure may serve both to improve function in the congested lung and to maintain PVR. Increasing ventilatory pressures, particularly PEEP, will require attention to maintaining adequate intravascular volume to support ventricular filling and avoid low cardiac output and systemic hypotension.

Rapid repetitions of non-invasive blood pressure monitoring should be continued until intra-arterial continuous blood pressure monitoring is available. Adequate monitoring of the circulation, respiration, and depth of anesthesia in these patients requires constant vigilance. It is advantageous to have at least one, and perhaps two, other pairs of experienced hands to perform the procedures required to prepare the patient for surgery after induction of anesthesia, so one anesthesiologist can focus on the monitoring and anesthesia.

Patients with ALCAPA who have been intubated, ventilated, and had appropriate vascular access obtained preoperatively may be sicker in many respects than the previous scenario, but the anesthesiologist will have to make less of a transition for the patient to anesthesia and establishing invasive monitoring and other preparation. It is still important that there is great vigilance in the transfer of the patient to the operating room and that the whole operative team is present ready to initiate CPB at short notice before the transfer commences. Patients who have already been placed on mechanical circulatory support present challenges in transfer, but providing there is no interruption to that support, they are very safely supported. The anesthesiologist must ensure the patient has adequate intravascular volume to allow good venous drainage into the external mechanical circuit. Monitoring the inlet pressure of the circuit can greatly assist this process.

Delivery of cardioplegia in patients with ALCAPA requires variation from routine procedures. Ensuring adequate cardioplegia flow to all the myocardium is crucial for the preservation of myocardial function. Usually this can be achieved by anterograde delivery of cardioplegia via both the normally placed right coronary and the anomalous left coronary, the latter usually achieved by cannulating and perfusing into the pulmonary artery clamped so that that flow is restricted to the ALCAPA vessel.

After the cross-clamp is removed and the heart is perfused, recovery of electrical and motor function of the heart may be slow. As long as the heart is not dis-tending, perfusion pressure and myocardial perfusion are adequate, allowing the heart considerable time to eject without the work of supporting the full circulation, which is beneficial for myocardial recovery. Forcing the heart to support the circulation with early weaning from CPB and administration of large doses of inotropes carries a high risk of return to CPB and of causing myocardial injury. TEE is crucially important in these infants to assess myocardial function and degree of MR after repair.

Translocation of a coronary artery has the major risks of bleeding from the suture line and poor flow in the coronary, leading to myocardial ischemia and poor function. Blood loss may be minimized by reversal of heparin (as far as possible, but may be limited by the need for mechanical support of the circulation), by optimizing coagulation with appropriate blood products and the
use of an antifibrinolytic. There is some evidence that aprotinin is the antifibrinolytic of choice in infants having CPB, but it is not available in some regions. Concern about thrombotic and embolic complications may deter some pediatric cardiac units from using these agents. Poor function of the translocated ALCAPA vessel may require revision of the surgery.

These patients are at significant risk for myocardial failure and circulatory collapse after weaning from CPB. Depending on the circumstances, leaving the sternum open and closing the skin with a membrane and dressing may be safer than formal closure of the chest. Not closing the sternum will prevent early pressure on the heart and allow room for some postoperative swelling without compression of the heart. The membrane closure also allows rapid access for resuscitation and return to bypass in the early postoperative period. Purse strings for cannulation for bypass may be left in place during this period and removed when the chest is formally closed. For patients who are less stable in the operating room, transitioning from a CPB circuit with venous reservoir to other mechanical support such as left ventricular assist device, biventricular assist device or ECMO will provide circulatory support of the patient while the myocardium recovers and improves function. Occasionally, failure to wean from CPB for other operations, i.e., ventricular septal defect (VSD) with left ventricular dilation and failure, may be due to an unrecognized ALCAPA; Callagan et al. reported this occurrence in a 6-week-old where pulmonary hypertension was suspected to have prevented severe left ventricular dysfunction, decreased the symptoms and masked the diagnosis of ALCAPA [28]. Coronary angiography confirmed the ALCAPA diagnosis, and emergency reoperation, repair of ALCAPA, and postoperative ECMO were necessary to ensure successful outcome.

**KEY POINTS: ALCAPA**

- ALCAPA presents with ischemic cardiomyopathy in the first few months of life.
- Decrease in PVR may create a coronary steal phenomenon.
- Early operation within days of diagnosis is recommended, due to the risk of sudden death.
- The risk of circulatory collapse at induction of anesthesia and in the pre-bypass period is high. Immediate institution of CPB should be available.
- Induction of anesthesia should be titrated with monitoring and cardiovascular support.
- Maintenance of both pulmonary and systemic vascular resistance (SVR) is important.
- Translocation of the ALCAPA to the aorta is the operation of choice.
- Availability and a reasonably low threshold for mechanical support (VAD/ECMO) are important considerations.

**Anomalous aortic origins of the coronary arteries**

Some of the abnormalities historically thought to be benign have more sinister subgroups where coronary perfusion may be jeopardized in certain circumstances and sudden death may occur. Abnormal origins of the coronary arteries from the aorta are most commonly benign; however, if these abnormalities involve a left coronary artery arising from the right coronary sinus (0.15% in adult cardiac catheterization series) and the course of the vessel passes between the aorta and pulmonary artery, then there is a risk of myocardial ischemia with angina and sudden death, especially with exercise. A right coronary artery arising from the left coronary sinus (0.92%) with the vessel passing between the aorta and pulmonary arteries is also associated with sudden death. Most of the variants of abnormal location of the origin of the coronary artery from the “opposite” coronary sinus do not have the vessel taking a course between the aorta and pulmonary artery and do not appear to be higher risk. Where the coronary artery does pass between the aorta and pulmonary arteries, it is postulated not only that exercise increases the risk of myocardial ischemia due to increased oxygen demand in the face of some obstruction to flow as a result of constriction between the aorta and pulmonary artery, but also that the increased cardiac output associated with exercise may cause distension of the root of these vessels, especially the elastic pulmonary artery, and worsen the obstruction of the coronary vessel “sandwiched” between the two great arteries.

Deciding about therapy is difficult in the scenario where the first symptom may be sudden death but the lesion may also be benign. Criteria for intervention are based on evidence of obstruction, symptoms, exercise testing, and detailed imaging to quantify lateral compression, and hypoplasia or stenosis associated with the anomaly, especially as there is commonly an intramural portion that may be narrow. Therapeutic approaches have included beta-blockers and/or advice to avoid exercise with substantial effort; cardiological intervention with stenting; and surgery, which may involve rerouting the vessel, unroofing a narrow intramural portion, or providing an alternative inflow by graft or aortic side-to-side anastomosis, distal to the narrow compressed segment [29,30].

**Congenital atresia of the left main coronary artery**

Congenital atresia of the left main coronary artery (CALM) is a rare, apparently benign anomaly. It is distinguished from “single coronary artery,” where the single vessel has two main branches with distributions similar to normal left and right coronary arteries, in that CALM has the distribution to the left heart filled retrograde by collaterals. There is an association with supravalvular aortic stenosis, especially Williams syndrome, with coronary anomalies,
Coronary arteriovenous fistulas: incidence, anatomy, and natural history

Coronary arteriovenous fistulas (CAVFs) occur in only 1 of 50,000 live births, but are noted in 1 of 500 patients having cardiac catheterization. In those with a congenital fistula, associated CHD occurs in 20–45%. Congenital fistulas may represent persistence of embryonic sinusoids that provide myocardial blood supply by cross-connecting the lumen of the primitive tubular heart. Although called “arteriovenous,” the distal connection is usually to the right side of the circulation but not necessarily to a vein, and termination in any chamber of the heart or in the pulmonary artery is possible. CAVF can also be acquired as a result of abnormal connections made by, for example, trauma, including surgery or cardiological intervention, infection, or ischemia.

Coronary arteriovenous fistulas may be subclassified by angiographic appearance as type A, where the coronary artery is dilated proximal to the fistula, but continues with the normal coronary vessel arborizing in the myocardium distal to the fistula; and type B, where the coronary artery is dilated over the entire length and terminates on the right side of the heart. These categories may determine management, as suitability for catheter occlusion and surgical approach will depend on the anatomy.

Coronary arteriovenous fistulas may present as incidentally detected asymptomatic murmurs. The natural history is very variable and largely depends on the size of the shunt created, the development of complications (see the next section) and associated conditions. Some smaller fistulas have been noted to close spontaneously [31].

Pathophysiology of CAVFs

Although often incidental findings, there are a number of mechanisms by which these anomalies can produce serious complications. As a connection between a high-pressure and a low-pressure part of the circulation, a high-speed turbulent jet may be created which may be the substrate for subacute bacterial endocarditis or for development of abnormalities of the supplying vessel, with fibrosis, stenosis, and aneurysm formation possible, and with consequent thrombosis, embolus, or rupture of a coronary vessel causing myocardial ischemia or sudden death. Myocardial ischemia may also arise from a coronary steal, with perfusion pressure in related coronary vessels becoming critically low due to the run-off down the sinus. If there is a high flow through the fistula, this may be sufficient to create significant volume loading with heart failure or pulmonary hypertension.

Surgery and catheter treatment of CAVF

There is controversy about whether asymptomatic fistulas should be treated, but some suggest that prevention of complications warrants intervention for all CAVFs. Others are more conservative, noting that spontaneous closure of some small fistulas has been observed and all interventions carry non-trivial risk and favor monitoring and conservative management. Some fistulas are suitable for catheter occlusion techniques if they are accessible and there is a low risk of coil embolus or interruption of distal coronary perfusion.

Surgical interruption of the fistula is the most common treatment. Some may be suitable for proximal ligation on the epicardial surface with a beating heart without CPB. Care must be taken to ensure that there is no myocardium that will become ischemic with ligation of the fistula. To preserve branches that provide myocardial perfusion, some fistulas will require ligation at their termination, which will usually require CPB.

Anesthesia for CAVFs

Anesthesia will be determined by the procedure planned and the complications that the patient has developed. If CPB and an open procedure are planned, the potential for the fistula to jeopardize myocardial protection must be carefully considered and managed. Run-off of the cardioplegia solution down the fistula may result in failure of myocardial protection for substantial segments of the myocardium. Controlling the fistula and then providing more cardioplegia may be warranted. Catastrophic failure of myocardial preservation has been seen to occur in cases where a fistula was undiagnosed or uncontrolled and where other associated congenital lesions were being repaired.

Coronary artery bridging, aneurysms, and stenosis

Coronary artery bridging represents a common normal variant, with the coronary artery having a segment of intramural course. Occasionally this may be associated with stenosis or dynamic occlusion, which may require intervention. It is rare for this diagnosis to be the primary indication for surgery in pediatric practice. In pediatrics, coronary bridging most commonly presents as technical problems for the surgeon, which may complicate surgery and be associated with coronary injury, sometimes producing ischemia and poor function after the surgical procedure.

Coronary aneurysms may be congenital, but acquired lesions due to Kawasaki disease are more commonly encountered in pediatric practice. It is rare that there are surgical or catheter interventions for these lesions, but anesthesia for imaging procedures may be required.

Congenital stenosis of the coronary arteries is rare. Lesions of the left coronary artery may be associated with sudden death. Acquired stenosis may occur in childhood as a result of precocious atheromatous disease in familial hyperlipidemia, secondary to abnormalities of the aortic root due to arteritis or connective tissue disorders, or in relation to fibrosis arising from turbulence due to regional anatomical abnormalities.
Coronary artery abnormalities associated with supravalvular aortic stenosis

Surpravalvular aortic stenosis, commonly associated with Williams syndrome, can result in abnormal coronary flow and sudden death. There are a number of case reports and series of these patients having circulatory collapse in association with anesthesia [32]. The most disturbing feature of these reports has been the absence of obvious precipitating factors, such as changes in heart rate or blood pressure. This has made anesthesiologists wary of these patients, because resuscitation has been unsuccessful in a number of these cases once cardiac arrest has occurred. These events are not well related to the degree of aortic obstruction, so the anesthesiologist may be falsely reassured that the risk is low, as with aortic valve obstruction of a similar degree.

The mechanisms for abnormal coronary flow in these patients are multiple [33]. There may be associated congenital abnormality of the orifice of the coronary arteries. There may be a proximal congenital stenotic segment of one of the coronary arteries, the left being the most dangerous. Turbulence related to the abnormal anatomy combined with systolic hypertension proximal to the supravalvular stenosis may lead to acquired changes in the coronary orifice with obstruction secondary to fibrosis or atheroma. Diastolic hypotension proximal to the supravalvular stenosis may decrease diastolic perfusion on which the left ventricle is dependent. Interaction between the tip of the aortic valves and the stenosed aortic segment may result in obstruction to coronary perfusion, either chronically or potentially acutely in relation to a fleeting change in valve disposition.

In summary, patients with supravalvular aortic stenosis are at high risk of acute coronary events that may be triggered by subtle changes in the circulation. Resuscitation may not be possible should cardiac arrest occur. Detailed cardiological evaluation may inform the level of risk, but avoiding anesthesia prior to surgical repair of the lesion may be warranted. The surgical plan should deal with both the supravalvular obstruction and the mechanisms of coronary obstruction. The anesthesia induction should be considered high risk, with immediate availability of emergency access to CPB. Further details about supravalvular aortic stenosis, and its anesthetic and surgical management, are presented in Chapter 21.

Pericardial effusion and tamponade

Incidence, anatomy, and natural history

The pericardium is a double-layered sac in which the heart and base of the great vessels are invaginated. There is normally a minimal amount of fluid between the inner visceral and tough outer parietal layers. There is enough compliance in this sac to accommodate small amounts of fluid collecting with minimal pressure change. In the acute situation, further fluid collection will be in the face of very low compliance and generate a rapid increase in pressure, which will compress the heart, preventing ventricular filling and decreasing stroke volume. In the more chronic situation, slow accumulation of fluid may allow time for expansion of the pericardial sac and larger volumes to be accommodated with less myocardial compression (than smaller volumes accumulating acutely). Chronic inflammatory conditions may induce fibrosis of the pericardium with decreased compliance of the pericardium and potential for a thick pericardium to tightly encase the heart, creating a chronic constrictive pericarditis [34,35]. Chronic pericarditis may be caused by tuberculosis.

Pericardial effusions have a large number of causes, including infections, particularly viral and Gram-positive bacterial, autoimmune disease, malignancy, uremia, trauma, and conditions associated with tissue edema and capillary leak, such as heart failure or the high venous pressures of a poorly functioning Fontan circulation [36]. In pediatric cardiac surgical centers, the commonest causes of cardiac tamponade are due to complications of surgical interventions. Cardiological interventions, such as the use of wires, balloon catheters and taking biopsies, and occasionally some anesthesia procedures, such as central venous cannulation, can all result in perforation of the heart and hemorrhage into the pericardium [37,38].

There are multiple mechanisms for pericardial collections to form as a result of cardiac surgery. Postpericardiotomy syndrome (PPS) may occur after 15–30% of open-heart procedures in children. The incidence is much lower, <2%, after closed procedures. The mechanism is immune-mediated with anti-heart antibodies almost always present. Previous suggestions that these reactions are commonly also linked to new or reactivated viral infections have been questioned in more recent studies. Although unpleasant and prolonging hospital stay, PPS only rarely leads to tamponade or death. Steroid prophylaxis does not prevent this condition in children and may lead to a worse course with an increased percentage needing drainage. Steroid treatment of PPS makes a modest impact on the recovery profile [39]. PPS is usually managed conservatively, but may occasionally need drainage of the effusion. Hemopericardium may arise from a specific source (or sources) of surgical bleeding, but it is more common for the postoperative bleeding to arise from raw surfaces, and conservative treatment, dealing with any clotting abnormality and having adequate surgical drains in place, will usually prevent the development of tamponade and the need for reoperation. If the bleeding persists or tamponade develops, surgical exploration will be required. Bleeding in relation to removal of surgically placed intracardiac vascular catheters and temporary pacing wires may occasionally be rapid and lead to cardiac tamponade. Protocols for close monitoring after line or lead removal, with elective echocardiography to look for an effusion some hours later (or earlier if there is a clinical suspicion of bleeding), have allowed earlier diagnosis of complications. Prolonged duration of effusion can occur in relation to lymphatic interruption, with the effusion being chylous if feeding has resumed. Patients who do not tolerate conversion to a completed Fontan circulation may also develop long-term effusions.
Pathophysiology and diagnosis of cardiac tamponade

The pathophysiology of acute pericardial tamponade involves myocardial compression with restriction of ventricular filling. Venous pressure is raised. As stroke volume decreases, sympathetic stimulation will produce tachycardia to maintain cardiac output and systemic vasoconstriction to maintain systemic blood pressure. Venous and end-diastolic ventricular pressure will rise as the tamponade progresses, and tachycardia and systemic hypotension will become more severe. The minimum pressure in any chamber or great vessel compressed by the tamponade will be the pressure generated by the tamponade, so pressures will equalize [40].

Further compromise to myocardial function during tamponade can arise due to myocardial ischemia, even in patients with normal coronary arteries. Severe tamponade will cause systemic hypotension and high end-diastolic ventricular pressure, which will produce a low coronary perfusion pressure. Tachycardia will be associated with a very brief diastolic duration, the only phase of the cardiac cycle where the myocardium of the left ventricle is perfused. This combination of low perfusion pressure and inadequate time for perfusion can create myocardial ischemia. This will decrease myocardial function, with both diastolic and systolic dysfunction exacerbating the systemic hypotension and increasing end-diastolic ventricular pressure, creating a vicious cycle of worsening myocardial perfusion.

Cardiac tamponade can occur with an open pericardium. The space where the fluid is confined and pressure is created, which compresses the heart, depends on the procedure that has been done. Most cardiac procedures done through a sternotomy will involve opening the pericardium, and many repairs of CHD require harvesting of autologous pericardium for use as surgical patches. Usually the pericardium is not closed with watertight suturing and it may be left widely open. In this circumstance, fluid collecting in the pericardium can emerge to occupy a larger space in the mediastinum. If drainage is inadequate, the physiologic consequences of cardiac tamponade will still develop once the space fills to the point of relative non-compliance and the pressure increases. Edema of the heart and mediastinal tissues in response to surgery and CPB may greatly decrease the volume and compliance of these spaces. Surgery may also have created continuity of this mediastinal space with the pleural spaces, which will allow large volumes of fluid to be accommodated in the pleura, decreasing the risk of tamponade but allowing greater concealed fluid (sometimes blood) loss. Draining the pleural fluid should also drain the mediastinal fluid in this scenario. In high-risk cases where chest closure is likely to create pressure on cardiac structures or vessels, or closure will create a small non-compliant space, with potential tamponade due to perioperative swelling, delayed chest closure can be used. The sternum is left open and the skin may be closed directly or by a membrane.

Clinical signs of cardiac tamponade include tachycardia and systemic hypotension and a high venous pressure. Beck’s triad is the combination of the hypotension and high venous pressure (distended neck veins in older children) with quiet sounds on cardiac auscultation [40]. Pulsus paradoxus, which is an exaggeration of the usual minimal (<10 mmHg) decrease in blood pressure with inspiration, increases with the degree of tamponade. Pulsus paradoxus can be quantified during auscultatory measurement of blood pressure by noting the difference between the pressure when the first Korotkoff sounds (which appear during expiration in the spontaneously breathing patient) and the pressure when the sounds become continuous. Other signs of sympathetic activation and low cardiac output, such as cool extremities and pallor from vasoconstriction, may be present. Clinical context will usually give some indication of the origin of cardiac tamponade. Obstruction of mediastinal/pericardial drains may be indicated by tamponade after cessation of previously consistent drainage.

Echocardiography provides a rapid, accurate detailed assessment of pericardial effusions. The site, size, and any evidence of loculation should be evident. This information can inform selection of the approach to drainage. The degree of myocardial compression and restriction of ventricular end-diastolic volume should also be apparent [41]. Other echocardiographic signs of tamponade physiology include IVC dilation and loss of respiratory variation in diameter of the vessel, increase of interventricular dependence with respiration, and respiratory variation of mitral, aortic, or tricuspid inflow peak velocity of >25%.

Surgery for pericardial effusion and cardiac tamponade

Ultrasound-guided, percutaneous drainage of pericardial effusion can be done with local anesthesia, especially in older cooperative patients. In patients in extremis due to tamponade, rapid drainage may be life-saving. If active bleeding is likely to be the source of the tamponade, open operation with surgical control of the bleeding will be required and appropriate maintenance of intravascular volume will be needed. For persistent pericardial effusions, surgical creation of a “pericardial window” by resecting a section of pericardium via an open subxyphoid approach can prevent collection of the fluid in the confined space of the pericardium. For the rare cases of chronic constrictive pericarditis, formal pericardectomy may be attempted, which is a substantial procedure with the potential for significant complications, such as hemorrhage, arrhythmia, and injury to the coronary arteries.

Anesthesia for pericardial effusion and cardiac tamponade

Ultrasound-guided drainage of a large pericardial effusion in a minimally symptomatic patient with local anesthesia should be a low-risk procedure, potentially performed without the support of an anesthesiologist. However, there is still the possibility of cardiac perforation or injury to superficial coronary arteries with consequent bleeding or myocardial ischemia. Areas of adhesion between
Drainage and retransfusion system for acute pericardial tamponade, which may improve cardiovascular reserve and allow minimal sedation and analgesia and local anesthetic, be appropriate to initially drain the pericardium with tamponade is relieved should be considered. It may be implemented, even if other parts of rapid-sequence induction of general anesthesia and institution of positive pressure ventilation. If there is evidence of significant tamponade, staged progress in anesthesia and surgery can be planned. Initial modest doses of sedation and analgesia, combined with local anesthesia, can allow percutaneous drainage of the effusion with relief of tamponade before the initiation of formal general anesthesia and controlled ventilation.

The highest-risk scenario is acute severe cardiac tamponade, usually due to postoperative hemorrhage in pediatric cardiac surgical centers, but also seen in trauma. The patient’s condition may be deteriorating rapidly and already be perilous. Rapid intervention is required but induction of anesthesia may precipitate cardiac arrest. A well-coordinated rapid team response is required. The patient’s underlying conditions and current status should be assessed. There may be time for resuscitation with intravenous fluids, inotropes, and vasoconstrictors to support the patient until the tamponade can be relieved and also to create some reserve to allow safer induction of anesthesia. If the tamponade is severe and resuscitation has already been attempted, the highest priority is facilitating rapid relief of the tamponade. The operating room team should be scrubbed and ready to proceed prior to anesthesia being induced. Blood for transfusion should be available and an appropriate anesthesiology team should be in place. If further intravenous access and (if the patient is stable enough) intra-arterial access are to be gained, multiple anesthesiologists/assistants may allow efficient and safe preparation of the patient. Induction of anesthesia can cause cardiovascular collapse by direct cardiac depression and vasodilation, as well as by decreasing the central sympathetic outflow. Even drugs with minimal direct depressive effects, such as fentanyl, can have a profound effect by this latter mechanism. Synthetic opioids are also prone to decreasing heart rate, which will also jeopardize the circulation. Positive pressure ventilation will exacerbate the problems with venous return and compression of the heart that have been created by the tamponade, increasing the chance of circulatory collapse.

The anesthesia sequence in these cases of severe tamponade needs to be tailored to the patient’s circumstances. Fasting status should be considered and cricoid pressure must be drained immediately; the highest priority is facilitating rapid relief of the tamponade. The operating room team should be scrubbed and ready to proceed prior to anesthesia being induced. Blood for transfusion should be available and an appropriate anesthesiology team should be in place. If further intravenous access and (if the patient is stable enough) intra-arterial access are to be gained, multiple anesthesiologists/assistants may allow efficient and safe preparation of the patient. Induction of anesthesia can cause cardiovascular collapse by direct cardiac depression and vasodilation, as well as by decreasing the central sympathetic outflow. Even drugs with minimal direct depressive effects, such as fentanyl, can have a profound effect by this latter mechanism. Synthetic opioids are also prone to decreasing heart rate, which will also jeopardize the circulation. Positive pressure ventilation will exacerbate the problems with venous return and compression of the heart that have been created by the tamponade, increasing the chance of circulatory collapse.

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Draining and retransfusion system for acute pericardial tamponade for cardiac perforation in the catheterization laboratory. The femoral venous sheath, if available, is the preferred site for reinfusion of blood. (Source: Mossad [43]. Reproduced with permission of Elsevier.)
Mitral valve leaflet distension, cleft, or restriction may lead to regurgitation. Distension of the valve, which may result from congenital structural abnormalities or may develop due to connective tissue disorders (e.g., Marfan syndrome) or inflammatory conditions such as rheumatic fever, can cause a portion of the valve to balloon beyond the plane of the annulus during valve closure (i.e., prolapse). This prolapsed portion is no longer in the plane of the annulus, leading to regurgitation. The anatomy of the mitral valve leaflets, anterior and posterior, is discussed in detail, highlighting the importance of maintaining the correct leaflet position during valve closure to prevent regurgitation.

Mechanisms of mitral valve regurgitation
Abnormalities of the annulus, leaflets, chordae, or papillary muscles may be associated with MR. Conditions that affect the left ventricle, such as aortic regurgitation and heart failure with eccentric left ventricular hypertrophy (e.g., dilated cardiomyopathy), may cause annular dilation. Dilation of the annulus increases the area requiring closure and decreases the area of the leaflet available for coaptation, both of which increase the mechanical stress on the valve tissue during systole, which may lead to immediate failure of coaptation and regurgitation or valve prolapse (see later) with subsequent regurgitation. A cleft in the annulus may not be able to be sealed by the leaflet tissue [46,47].

Mitral regurgitation
Incidence, anatomy, and natural history of MR
Isolated MR is an uncommon pathology in childhood. The atrioventricular valve serving the systemic ventricle is not considered a mitral valve in the relatively common atrioventricular septal defect, univentricular hearts and in patients with “congenitally corrected transposition of the great arteries” (i.e., combined atrioventricular and ventriculoarterial discordance). Abnormalities of these “non-mitral” left atrioventricular valves are discussed in the relevant chapters (see Chapters 24 and 25 for further discussion).

Normal anatomy and function of the mitral valve
The normal mitral valve allows low resistance passage of blood from the left atrium to the left ventricle during ventricular diastole and prevents blood returning from the left ventricle to the left atrium during ventricular systole. Abnormalities of the valve can result in restriction of forward flow (stenosis) or return of blood from the left ventricle to the left atrium during ventricular systole (regurgitation or incompetence). MR and stenosis may occur in combination [44] (Figure 26.13).

The mitral valve consists of an annulus, leaflets, chordae, and papillary muscles. The annulus is part of the continuous fibrous framework separating the atria and ventricles. There are two mitral valve leaflets, anterior and posterior. The leaflets are not symmetrical. The posterior (mural) leaflet is attached to 210 degrees of the circumference of the annulus, where it is continuous with the left ventricular free wall. The anterior (septal) leaflet is attached to the portion of the ring continuous with the septum and aortic valve over about 150 degrees. The anterior surface of the anterior leaflet is thus the posterior surface of part of the left ventricular outflow. On closure of the mitral valve, the posterior leaflet forms a crescentic (“C”-shaped) part of the closure of the annulus, contributing only about a third of the cross-section of the closure despite the whole leaflet being much larger than the anterior leaflet. The smaller anterior leaflet contributes the remaining, more oval, two-thirds of the closure of the annulus. This arrangement of the valve leaflets means that the posterior leaflet leaves little space between the free wall and the leaflet during systole and the anterior leaflet moves towards the posterior leaflet, increasing the diameter of the left ventricular outflow during systole. The crescentic portion of the posterior valve and the oval portion of the anterior valve, which close off the annulus, are a relatively small proportion of the total surface area of the valves. During mitral valve closure, a significant proportion of the surface area of the valves lean on each other, thus providing “mutual support” during closure. This coaptation of the valve leaflets decreases the tension in the valve tissue required to maintain valve closure. The valve leaflets have multiple fibrous bands, chordae tendinæ, which connect them to both the papillary muscles (anterior and posterior), projecting from the inner wall of the mid-left ventricle. The chordae connect to both the surface and edge of the valve leaflets, distributing the forces of systolic papillary muscle contraction over a wide area of the valve leaflets [45].

This maneuver can be life-saving as preparations are made for sternotomy and repair of the perforation [43] (Figure 26.12).

In postoperative patients in the intensive care unit with circulatory collapse secondary to cardiac tamponade, rapid reopening of the sternum in the unit may be life-saving,
supported by the opposing valve and, as with aneurysms, the law of Laplace will apply and wall tension will rise as the prolapse progresses and tend to make that region expand until the valve fails to oppose or even ruptures. Restriction of leaflet movement, such as with fibrosis due to inflammation, may prevent a leaflet coapting with the opposing leaflet and consequent regurgitation. Similarly, elongation of the chordae may cause leaflet prolapse while shortening, and fibrosis may cause restriction of leaflet movement, with regurgitation developing in both scenarios. Rupture of chordae may cause acute regurgitation. Fibrosis of either leaflets or chordae also tends to be associated with stenosis of the valve. Elongation of papillary muscle can cause valve prolapse and regurgitation of the mitral valve. Papillary muscle dysfunction may also cause MR. For example, in dilated cardiomyopathy, poor contraction and elongation of the papillary muscles and consequent leaflet prolapse will often be exacerbated by annular dilation and cause marked MR. Specific papillary muscle dysfunction can arise in relation to coronary artery problems, as the blood supply of the papillary muscles is usually from separate coronary arteries. Mistiming of papillary contraction in relation to the rest of ventricular contraction may be associated with MR. This may occur with some abnormalities of the coordination of timing of regional contraction, such as conduction disturbances, some arrhythmias and complications of pacing of the ventricle. Other rare causes of MR include distortion of the valve apparatus due to tumors [48].

Many of the conditions associated with MR can affect multiple areas of the valve apparatus (annulus, leaflets, chordae, papillary muscles) and compound the problem. Fusion of the valve leaflets at the commissures is usually associated with stenosis rather than regurgitation.

In adults the commonest mechanism of MR is mitral valve prolapse, which is usually asymptomatic, and often presents incidentally with an auscultatory click and murmur. The earliest phase of this may be “superior systolic motion” of mitral leaflet tissue above the plane of the annulus. In clinically normal children, this echocardiographic sign increases in frequency from around 1% in infants to nearly a quarter of 6- to 10-year-olds and more than a third of 11- to 18-year-olds. Some of these cases may progress to prolapse and significant regurgitation, but, given the benign outcome in most, isolated superior systolic motion is usually considered a variation of normal.

Rheumatic cardiac disease is common on a world scale and, although appearing sporadically in a wide range of communities, is commonest in socioeconomically disadvantaged communities with a high incidence of streptococcal infection and poor general health. The highest incidence of rheumatic fever in the world is said to be in the indigenous communities of remote Australia. MR is the commonest rheumatic valve lesion in children with this condition, with mitral stenosis appearing later in the disease progression, and involvement of other valves, such as the aortic, being less common initially. Public health measures for prevention of rheumatic fever are the most important long-term approach. Valve-preserving reconstructive surgery has a number of advantages for children with rheumatic MR, avoiding the need for replacing an artificial valve due to growth and the need for anticoagulation (which may be difficult to manage in many of the communities with the highest incidence of rheumatic fever).

Mitral regurgitation tends to be a progressive condition, as the regurgitation volume loads the left ventricle, which will dilate, exacerbating the regurgitation. Children who have successful surgical repair of MR tend to have
recovery of ventricular function and good long-term outcomes. There is an association between longer-term presence of regurgitation and atrial arrhythmias, which may continue or arise after repair. This is associated with chronic enlargement of the left atrium, which may be addressed in high-risk cases at the time of surgical intervention for the regurgitation.

Pathophysiology of MR
Mitral regurgitation will tend to worsen with time unless the underlying pathology is corrected. The presence of regurgitation results in the need for bigger end-diastolic volumes if an adequate forward flow (cardiac output) is to be maintained as well as accommodating the regurgitant fraction, which returns through the mitral valve during systole. Increased left ventricular end-diastolic volume (LVEDV) will promote dilation of the annulus which will tend to increase the regurgitant fraction, thus creating a disadvantageous positive feedback loop of increasing regurgitation and dilation of the left ventricle, until ventricular dysfunction is superimposed on the process, which will result in decompensation of the cardiovascular system.

Mitral regurgitation is exacerbated by factors that increase left ventricular afterload and volume loading. Lessening SVR and relieving aortic valvular abnormalities (either stenotic or regurgitant) will tend to decrease MR. If myocardial ischemia is contributing to papillary muscle dysfunction, this may be resolved by restoring coronary artery blood flow. In some cases, MR can resolve without mitral valve surgery, if the underlying precipitating factors are resolved. The onset of atrial arrhythmias, such as atrial fibrillation, associated with left atrial dilation due to MR, may trigger cardiovascular decompensation. Persistent severe MR, especially in association with the onset of ventricular dysfunction and the associated very high left ventricular end-diastolic pressures, may cause significant pulmonary hypertension with impairment of right ventricular function. Right ventricular function may also be impaired by the dilation of the left ventricle, which causes ventricular septal shift towards the right ventricle.

Surgical approaches and outcomes for MR in children
The advent of high-quality echocardiography, including 3D imaging of the mitral valve, has contributed greatly to the understanding of the mechanisms of MR. Surgical repair can now address all levels of factors contributing to regurgitation [49].

Thus the annulus can be supported or decreased in size with a number of techniques, including insertion of a supravalvular ring [44] (Figure 26.14). The leaflets can be modified to prevent prolapse, have patches inserted and fibrotic areas debulked, improving coaptation and movement. Fusion of commissures where valve leaflets have joined may need to be freed to allow adequate valve movement and to relieve stenosis, but more complex repair may be required if commissurotomy creates a cleft or failure of coaptation. Chordae can be reimplanted or changed in length, and papillary muscle elongation shortened. The aim of avoiding valve replacement is realistic for most pediatric cases. Mitral valve replacement has higher long-term mortality than any other valve replacement in children; infant mitral valve operative mortality has been reported to be 5–52%, and 5- and 10-year survival rates to be 33–95% [50]. The benefits of valve repair over replacement include avoiding the need for anticoagulation, the need for replacement of the artificial valve with growth in smaller children, and the high risk of mitral valve replacement in babies. In this last group, there is a lack of very suitable artificial valves and the surgery is complicated, as the artificial valve ring may need to sit above the annulus and the body of the artificial valve may still impair ventricular function. The lack of papillary muscle connection to the artificial valve is also associated with an abnormal geometry of ventricular contraction, which may contribute to worsening ventricular function. Complex valve repairs have been enabled by modern techniques for myocardial preservation that allow long cross-clamp times to be well tolerated with good postoperative myocardial function.

For children with underlying conditions, which may continue or recur, such as connective tissue disease or rheumatic fever, there is a significant risk of recurrence of MR. Time gained in growth before an artificial valve is required is often a great advantage, and repeated surgery for repair of the native valve may still be a reasonable management plan in children.

Surgery is best timed before there is severe chronic dilation of the left ventricle with loss of function, although follow-up studies in children suggest that successful repair is associated with good recovery of function over the long term. Chronic left atrial dilation is associated with atrial arrhythmias, which may persist or commence postoperatively.

Anesthetic considerations for repair of MR
Functional assessment of the MR is based on history of activity and exercise tolerance, and is a robust measure of cardiorespiratory reserve. In infants, cardiac failure may be indicated by breathlessness and sweating with feeding, and poor weight gain. Physical examination should not only elicit the pansystolic murmur typical of MR but also seek signs of complications such as an enlarged left ventricle, or cardiac failure with a third heart sound and evidence of pulmonary congestion. History and examination may also indicate underlying conditions that may have caused the MR, such as rheumatic fever or Marfan syndrome, as well as signs of other associated cardiac lesions. Echocardiography can provide information about the severity of the regurgitation, associated lesions, and myocardial function [51]. Understanding the mechanism for the regurgitation is crucial for planning the surgical
approach to repair. Standard “adult” echocardiographic measures to quantify MR may not be applicable to small pediatric patients and assessment of the severity may require interpretation rather than being able to be precisely quantified. Factors include the diameter of the base of the regurgitant jet, the shape and distance that the regurgitant plume penetrates into the left atrium, whether there is retrograde flow generated in the pulmonary veins, and left atrial dilation as well as estimates of the regurgitant fraction (compared with total ejection of the ventricle). Standard estimates of myocardial function may be difficult to interpret in the presence of a dilated ventricle. The increase in volume that occurs with ventricular dilation, proportional to the third power of the diameter, means that a greater volume change occurs with a change in diameter at larger diameters. Therefore, when the dilated ventricle is full, the change in volume with contraction is very much larger than the change in volume caused by a similar decrease in diameter at a smaller starting volume. Thus, apparently small movements of the dilated ventricle may be associated with substantial volumes of ejection. Measures of tissue acceleration or initial rate of change of pressure over time may reflect underlying myocardial function better than measures of ejection fraction. Measures of ejection fraction are also complicated by the fact that there are separate “forward flow” and regurgitant fractions and that the regurgitant fraction can be considered a low resistance pathway and decreases the afterload of the ventricle (this “afterload” reduction arising from the retrograde regurgitant flow). The presence of this low-resistance pathway may also influence functional measures of contraction, in that the rate of contraction may be increased compared with ejection into a higher resistance system.
Patient management up to the time of presentation should also be assessed. Medical therapy for MR with systemic vasodilators such as angiotensin-converting enzyme inhibitors can decrease the regurgitant fraction. Systemic vasodilatation will change the balance in favor of “forward flow” compared with regurgitation. Systemic vasodilatation, often aided by diuretic therapy, can decrease end-diastolic ventricular volume, which may further reduce regurgitation by decreasing the size of the annulus. Improvements of echocardiographic measures of MR have been noted after a first dose of captopril. Optimizing medical therapy and nutrition should provide more cardiorespiratory reserve for the patient at the time of surgery.

In patients with MR and well-preserved myocardial function, anesthesia is usually well tolerated. Anesthesia induction should avoid increases in SVR. Increased SVR will increase the regurgitant fraction and jeopardize forward flow. Heart rate should be maintained, as the increased LVEDV associated with bradycardia will worsen MR. Excessive intravascular volume loading may also worsen MR by increasing LVEDV and distending the annulus. Positive pressure ventilation and positive end expiratory pressure should improve respiratory mechanics by decreasing lung congestion and optimizing functional residual volume. Cardiovascular performance should also be favorably influenced, as positive pressure ventilation will tend to increase left atrial pressure and decrease the afterload of the left ventricle, both of which should improve cardiovascular performance in patients with MR.

Monitoring should be as for any pediatric CPB procedure. In patients with severe MR and cardiac dysfunction, surgically placed pulmonary artery and left atrial lines may be warranted for the post-repair phase. TEE is very helpful in both planning and assessing the surgical repair, but can also be a useful monitor to inform decisions about strategies to support the cardiovascular system.

In late presentations of MR, with myocardial dysfunction and pulmonary hypertension, or patients with associated lesions such as mitral stenosis, the risk of cardiovascular decompensation with anesthesia is greater. Apart from having less reserve, some conditions may do better with an opposite strategy to that which is optimal for MR. For example, maintaining, and even increasing, SVR will benefit patients with mitral stenosis, whereas decreasing SVR is an aim for patients with MR. The more severe the cardiovascular disease and the more complex the associated conditions, the more tightly the circulation should be monitored, and titration of anesthesia drugs, cardiovascular agents, and ventilation strategies should be constant to maintain a stable circulation. In pure MR with cardiovascular decompensation, an inotillator such as milrinone or low-dose dobutamine may be useful to provide both low SVR and improved contractility.

Most cases with isolated MR and preserved myocardial function who have successful repair of the lesion and high-quality myocardial preservation during the aortic cross-clamp phase will tolerate the procedure well and are likely to be candidates for early extubation after the procedure. The commonest issue with these patients in the postoperative phase is that the good function with a dilated left ventricle creates an almost obligatory large stroke volume, which may create significant systemic hypertension. Systemic vasodilation and avoiding tachycardia may be indicated. Appropriate sedation and analgesia will assist these aims. Centrally acting α2-adrenergic agents such as clonidine or dexmedetomidine may be useful supplements in this phase, contributing to sedation, analgesia, systemic vasodilatation, and a tendency to a low heart rate. More complex cases with poor function and associated lesions or residual valve lesions will usually require more support and a longer intensive care course.

 Patients with poor function and residual regurgitation in the early postoperative phase may have a decrease in the regurgitation as function improves. This may relate to decreasing ventricular dimensions with improved function, which decreases the size of the annulus, and to improvement in papillary muscle function, stabilizing the leaflets and decreasing prolapse. This may influence the judgment of when immediate revision of the repair is indicated when the intraoperative post-bypass echocardiography demonstrates residual regurgitation. This judgment is also informed by the mechanism of the residual regurgitation, as some mechanisms may be clearly mechanical (rather than “dynamic”) and reparable with further surgery, and unlikely to improve without surgical intervention.

**KEY POINTS: ANESTHESIA FOR MR**

- Isolated MR is uncommon in childhood.
- Associated conditions such as rheumatic fever or connective tissue disorders and other valve lesions should be sought.
- Repair rather than replacement of the valve is the usual aim in childhood.
- Pre-bypass, anesthesia technique should aim to avoid increases in SVR and bradycardia, which will both increase the regurgitant fraction.

**Cardiac tumors in childhood**

**Incidence, anatomy, and natural history**

Cardiac tumors are rare in childhood. Even major series based on large populations over long periods of time have quite small numbers of cases (tens rather than hundreds) [52]. The incidences reported vary hugely, as the origins of the series are very varied, such as surgical case series, pathology, oncology, and fetal ultrasound screening databases, and the relevant population is often difficult to estimate. Depending on the definition used, any mass in the heart can be described as a tumor. This discussion will exclude thrombus, vegetations, and other inflammatory masses, but it is important to consider these...
in the differential diagnosis of a mass under investigation. Tumors included will be those generated by an abnormal growth of cells that are localized and not part of the normal anatomy and physiology of the heart. Pathologically, cardiac tumors can arise as primary growths from any tissue in the heart, which can include complex multi-tissue structures such as hamartomas, which may be benign or malignant. Cardiac tumors can also arise from local spread of malignancy in adjacent tissues or secondary deposits from remote tumors. The cardiac anesthesiologist may also be confronted with patients with tumors external to the heart that have grown extensions down the venous system towards, and sometimes into, the heart, which are only attached at the base at the tissue of origin. These are not technically “cardiac tumors.” They may require CPB for excision and most frequently involve Wilms’ tumors, but can also occur with rhabdosarcoma.

The significance of cardiac tumors will depend on their position and functional consequences and the natural history of the particular tumor. Significant functional effects include obstruction, occasionally of an intermittent ball valve nature with lobulated masses, conduction disturbances and arrhythmia generation, thrombotic and embolic complications, the emboli being potentially either clot or tumor, and involvement of the pericardium with effusions and tumor infiltration. Pericardial involvement is most commonly an extension of mediastinal lymphoma or germ cell tumors, both of which are primarily treated medically, although surgical intervention for biopsy, drainage of effusion, or debulking of tumor may be required. The prognosis of secondary malignant cardiac tumors is usually poor and based on the progression of the malignancy, including elsewhere in the body.

The most common cardiac tumor of children is rhabdomyoma, comprising more than half the cardiac tumors in most pediatric series [53] (Table 26.2). Rhabdomyoma is most commonly associated with tuberous sclerosis. This autosomal dominant condition with variable penetrance is mostly related to abnormalities in either of two genes, TSC1 and TSC2, which code for the proteins hamartin and tuberin. TSC1 and TSC2 are tumor suppressor proteins. About two-thirds of cases of tuberous sclerosis arise from new mutations, and about 80% of cases have an identifiable abnormality in TSC1 or TSC2. Tuberous sclerosis affects many tissues in the body and the abnormal growths comprise a wide range of pathological subtypes. The lesions in the brain usually have the most profound clinical effects, while kidney, liver, and lung lesions are also clinically significant; when present, the typical facial “adenoma sebaceum” (actually angiofibromas) are a prominent clinical sign not always associated with tuberous sclerosis. The cardiac rhabdomyomas appear in the second half of pregnancy and tend to regress after birth. As many as 90% of patients with tuberous sclerosis may have cardiac tumors at birth, but the figure decreases to about 20% in adults. There may be multiple cardiac rhabdomyomas in patients with tuberous sclerosis. The possibility of medical therapy for clinically significant cardiac rhabdomyomas has recently arisen. The abnormal proteins produced by the abnormal genes associated with tuberous sclerosis affect a protein called “mammalian target of rapamycin” (mTOR), which is a controller of cell proliferation. Inhibitors of mTOR have been used in oncology and transplant immunosuppression to suppress cell proliferation. One of the mTOR inhibitors, everolimus, has been reported to be effective in a case of clinically significant multiple cardiac rhabdomyomas in an infant [54]. This followed another report of regression of a stable cardiac rhabdomyoma in a 7-year-old with tuberous sclerosis who received everolimus for treatment of a subependymal giant-cell astrocytoma, a brain tumor associated with tuberous sclerosis.

Fibromas, probably hamartomatous in nature, are the second most common cardiac tumor of childhood. These are slow-growing or stable in size and the need for intervention will be decided by a balance between symptoms and the risks of surgery, given the specific anatomy of the lesion. They are most commonly ventricular. There is less risk of embolic complications than with myxomatous lesions. Incomplete resection may be a reasonable aim if palliation of, for example, obstruction is required, but an attempt at complete removal would jeopardize long-term cardiac function.

Atrial myxomas are the commonest primary cardiac tumor in adults, but they occur rarely in children, and almost never in neonates or infants. One series of 112 patients with myxoma had no female child patients and the youngest male was 5 years old and the majority were over 50 years old. The left atrium is the commonest site for these tumors (75%) and presentation is usually due to obstruction of the mitral valve (about two-thirds) or embolism (about one-third), while non-specific systemic signs such as fever and malaise also occur in about a third of patients. Carney complex, and associated LAMB and NAME syndromes, is a rare genetic condition where myxomas may present in younger patients and may be multiple in association with skin lesions and endocrine abnormalities, such as Cushing’s syndrome and other, usually endocrine, tumors.

Teratomas are uncommon, midline tumors that may present early in life, with the mediastinum being the

### Table 26.2 Primary benign cardiac tumors in children

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Age, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhabdomyoma</td>
<td>28 (62) 35 (45)</td>
</tr>
<tr>
<td>Teratoma</td>
<td>9 (21) 11 (14)</td>
</tr>
<tr>
<td>Fibroma</td>
<td>6 (13) 12 (15.5)</td>
</tr>
<tr>
<td>Hemangioma</td>
<td>6 (2) 4 (5)</td>
</tr>
<tr>
<td>AV node mesothelioma</td>
<td>1 (2) 3 (4)</td>
</tr>
<tr>
<td>Myxoma</td>
<td>– 12 (15.5)</td>
</tr>
<tr>
<td>Neurofibroma</td>
<td>– 1 (1)</td>
</tr>
<tr>
<td>Total</td>
<td>45 (100) 78 (100)</td>
</tr>
</tbody>
</table>

AV, atrioventricular.
Source: Lange et al (53) reproduced with permission of Wiley.
second most common site after sacral teratoma. The majority are not malignant and surgical resection is the usual treatment. Although usually arising above the heart in the anterior mediastinum, the heart and great vessels may be involved in these sometimes very large masses, which may make resection difficult or impossible and some procedures may require CPB. In utero fetal surgery has been successfully performed for mediastinal teratoma.

Hemangiomas can occur anywhere in the heart and may be asymptomatic, may regress, and may respond to medical therapy. Depending on the position and complications, some will require surgical resection. Some can present in infancy. There have been major advances in understanding the biology of various forms of hemangioma, and prognosis and treatment are evolving. If surgery is not required urgently, cardiac hemangiomas should be assessed by an expert vascular malformation clinic, as medical therapy may be available and detailed prognostic information may be attainable, particularly with regard to the possibility of spontaneous regression.

**Pathophysiology of cardiac tumors**
The natural history of the different tumor types will determine the progression of the cardiovascular effects of cardiac tumors. Rhabdomyomas tend to act as mass lesions that may disturb the efficacy of myocardial contraction, create stenosis or valve incompetence, or disturb the conduction system. The possibility of regression will make observation a reasonable management option in many cases with minimal symptoms. This is in contrast to myxomas, which are most commonly pedunculated, with a marked tendency for both tumor and clot embolus, and which eventually cause obstruction, most commonly of the mitral valve if based in the left atrium. Fibromas are often smooth finger-like projections, which may remain asymptomatic for long periods and eventually stabilize or regress in size.

The cardiovascular pathophysiology of cardiac tumors must be assessed on a case-by-case basis, with clinical history and signs combining with investigation, particularly echocardiography, to define the lesion and the impact on the circulation. MR imaging and angiography can allow both dynamic and detailed 3D reconstruction, with more detailed distinguishing of the different tissues than is available with echocardiography. Electrocardiography with Holter monitoring may be required if arrhythmia is suspected.

**Surgical approaches and outcomes for cardiac tumors**
Surgical planning and decision-making for cardiac tumors will depend on the following factors: tumor type, tumor position and pathophysiologic effects, and the risks of excision. Most procedures for cardiac tumors will involve CPB, but occasional lesions involving structures that do not require opening of the heart may not. Sternotomy is the usual approach, but various less invasive approaches have been used for tumors such as atrial myxoma where the lesion is pedunculated and the surgery can be performed through a left thoracotomy or partial sternotomy.

For pedunculated intravascular tumors that have grown into the heart along the great veins (e.g., a Wilm’s tumor), but which are not attached to the heart, strategies to deal with the intravascular tumor, prevent embolization, and have adequate CPB may require tailoring of the perfusion plan to the exact anatomy and include having venous drainage from sites external to the heart (Figure 26.15).

If cardiac tumors can be removed without disrupting the postoperative function of the heart, outcomes are usually good. The degree of resection attempted will be informed by this, as partial resection may be preferable for rhabdomyomas and fibromas if more radical surgery will jeopardize the outcome. As these tumors are slow-growing, or tend to stabilize and even regress, partial resection that relieves symptoms will often be adequate. Atrial myxomas are occasionally locally aggressive and may recur if the base is not adequately excised. The outcome for surgical excision of myxomas is usually very good, but the occasional child with myxoma is more likely to be in the higher-risk familial, genetic group, which is more likely to recur both locally and at a separate cardiac location.

Teratomas arising at the base of the heart may be large and grossly distort and involve the great vessels and the coronary arteries. Surgery may be extremely difficult technically and a multidisciplinary team involving cardiology, medical imaging, cardiac surgery, oncology, perfusion, and anesthesia should carefully plan the approach to excision.

**Anesthesia considerations for cardiac tumors**
Anesthesia for the wide range of possible procedures relating to cardiac tumors needs to be tailored to the patient’s condition and the planned surgery. Most rhabdomyomas will not require surgery, but those that do will usually have a significant cardiovascular impairment which will need to be defined. Patients with tuberous sclerosis are likely to have multiple other systems involved and behavioral issues such as developmental delay and autism that will require special attention to minimize distress for the patient and family.

Tumors that involve the right side of the heart and pedunculated lesions that have passed centrally from peripheral origins may require consideration with regard to where vascular access is placed, with lesions involving the inferior vena cava (such as venous extension to the atrium of Wilms’ tumor) having vascular access in the upper limb and avoiding femoral central access, while lesions arising in the neck and upper limbs (which are less common but can occur with rhabdomyosarcoma) require lower limb vascular access.

Patients with malignant lesions involving the heart will have often received chemotherapy. Complications of these therapies should be assessed. Bone marrow status
should be checked to confirm or plan for appropriate recovery or management of anemia, thrombocytopenia, and neutropenia. Consideration should be given to previous use of agents that sensitize the lungs to hyperoxia, such as bleomycin, or those with potential for cardiotoxicity, such as adriamycin, and to assessing the patient’s current status in relation to those issues. Surgery is rarely indicated for malignant lesions not arising in the heart, but debulking recurrent lymphoma that has invaded the pericardium from the anterior mediastinum is occasionally required. These recurrent lesions involving the pericardium are rarely of a size or in a position to create the issues described in the section on anterior mediastinal masses. Those scenarios are much more likely at first presentation. Lymphomatous pericardial effusion may also need drainage either for diagnostic purposes or to relieve tamponade. Careful assessment and management of the patient with potential for tamponade are required (see previous section).

Teratomas arising in the midline at the base of the heart will usually be present at birth and may be very challenging for all clinicians involved. The patient’s preoperative condition may be very poor, with obstruction to major vessels, distortion of the heart and coronary vessels, and potentially high-output cardiac failure and persistent pulmonary hypertension due to the large blood supply of the lesion. Excision without injuring important cardiac structures, leading to postoperative dysfunction (such as coronary artery damage), may be difficult and intraoperative blood loss may be extensive and difficult to control. Appropriate planning to support massive transfusion and prevention of coagulopathy is appropriate.

Anesthesia may be required for interventional imaging procedures to define, biopsy or occasionally treat tumors of the heart.

**KEY POINTS: ANESTHESIA FOR CARDIAC TUMORS**

- The commonest cardiac tumor in childhood is the rhabdomyoma.
- Fibromas are usually discrete and surgery is aimed at relieving whatever complications have arisen.
- Myxomas are the commonest intracardiac tumor in adults, but they are rare in children.
- Teratomas are midline and may arise at the base of the heart and present as large tumors in the neonatal period.
- Malignant tumors involving the heart are rare and have a poor prognosis.
- Cardiopulmonary bypass may be required for pedunculated tumors that have grown along venous paths to the atrium, such as a Wilms’ tumor.
- Anesthesia for cardiac tumors is based on the preoperative patient condition and the nature of the surgery planned.
Aortic aneurysm and aortopathy in children

Classification and definition of aortic aneurysms
Aortic aneurysms are localized dilations of the aorta anywhere from the aortic valve ring to the bifurcation of the aorta [55]. True aneurysms involve all the layers of the vessel wall (intima, media, and adventitia). Fusiform aneurysms involve dilation of the whole diameter of the vessel and may involve a considerable length of the vessel. This is the most common form for aortic aneurysms. Saccular aneurysms involve a berry-like expansion, sometimes with a narrow neck at a weak spot in the vessel wall. Aneurysms of a single sinus of Valsalva are saccular.

A false aneurysm is usually secondary to local pathology such as trauma or infection and involves the creation of a space in continuity with the inside of the vessel. A false aneurysm is not bounded by the vessel layers but by external tissue, such as the wall of an abscess that has eroded the vessel or the site of previous trauma where organized clot and fibrosis now contain the false aneurysm.

Dissecting aneurysms occur when an aneurysm, usually fusiform, creates an intimal tear, sparing the adventitia and sometimes the media. The arterial pulsations then split the internal layers, creating a blood-filled space in the wall of the vessel which tracks the vessel and continues to split the layers apart, still leaving the adventitia intact. The dissection may rupture internally by tearing the intima at another site or eventually rupture the adventitia. The dissection process may occlude branches of the vessel and be the site of thrombosis and a source of embolus.

Incidence, anatomy, and natural history of aortopathy in children
Aortic aneurysms are rare in childhood and can be classified according to the site, type, acuity, and underlying pathology. False aneurysms occur at the site of trauma, including as a complication of surgery or needle puncture, and due to infection, such as mycotic aneurysms. Dissection of the aorta is rare in childhood and, if it occurs, tends to occur later in childhood in patients with underlying connective tissue disorders with large fusiform aneurysms.

The vast majority of pediatric aortic aneurysms involve the ascending aorta and the aortic root. The transverse arch, descending thoracic aorta, and abdominal aorta are rare sites of aneurysm formation in children. The commonest causes of aneurysms of the ascending aorta and root of the aorta in children are genetic conditions, especially connective tissue disorders, with Marfan syndrome being the most common of these. Inflammatory conditions such as autoimmune disease and arteritis may also affect the aorta and be associated with aneurysm formation. Inflammatory conditions such as Takayasu’s arteritis or Kawasaki disease will usually have multifocal arterial lesions, often stenotic, as well as other features, such as systemic illness, with aortic aneurysm as an occasional complication. There is a growing understanding of a relationship between various congenital cardiovascular malformations and abnormalities of the ascending aorta, with the term aortopathy being applied to these changes.

Rupture of an aortic aneurysm is usually rapidly fatal due to hypovolemia. Saccular and false aneurysms and aneurysmal dissections may be niduses for thrombosis and the source of emboli. Branches of the aorta may be occluded by dissection of an aortic aneurysm, with ischemic consequences to distal tissues.

Genetic conditions associated with aortic aneurysm
Marfan syndrome
Marfan syndrome is the most significant genetic condition associated with aneurysm of the aorta, usually involving the ascending aorta and often the aortic root [56]. The clinical diagnosis of Marfan syndrome is based on the revised “Ghent” criteria [57]. The revision in 2010 put more emphasis on aortic dilation (z-score ≥2) as the key to diagnosis. Variations based on the presence of a family history and the age of the patient are included. The existence of related syndromes, including ones with aortic dilation but differing genetics and a spectrum of either differing or overlapping (with Marfan) associated features, such as Sprintsen–Goldberg syndrome, Loeys–Dietz syndrome, and the vascular form of Ehlers–Danlos syndrome, are specifically included in the diagnostic process to make misdiagnosis less likely. The clinical features and genetic differences can distinguish these and a number of other rarer syndromes. “Typical” patients with Marfan syndrome will often have particular facial features and body habitus with long thin limbs, tall stature, and hypermobility of joints. Arachnodactyly can be demonstrated by the thumb sign (the adducted thumb has the whole of the nail protrude beyond the ulnar margin of the palm) and the wrist sign (when encircling the opposite wrist, the thumb and fifth finger overlap). These and many other physical signs are codified in the Ghent criteria.

Marfan syndrome has an incidence of about 1 in 10,000 and is an autosomal dominant condition with variable penetrance [56]. About 25% of cases involve new mutations with some effect of parental age. Mitral valve regurgitation may also occur, often earlier than the aortic dilation but usually with less severe consequences. Aortic regurgitation is usually secondary to aortic root dilation. Skeletal and ophthalmic abnormalities are the main other features of the syndrome. The abnormal gene in most patients with Marfan syndrome is FBN1, which lies on chromosome 15 and encodes for type 1 fibrillin, a protein with 2,871 amino acids which forms part of the microfibrils in the extracellular matrix [58]. There are a large number of mutations of FBN1 that cause the syndrome, most of them altering a single amino acid. The phenotype produced is highly variable and does not correlate well with the
different mutations. There are also a series of related “fibrillinopathies” with associated genetic abnormalities that give rise to variants of Marfan syndrome; these may not have all the clinical features of Marfan syndrome but some are associated with aortic aneurysm. There is a rare neonatal form of Marfan syndrome. Although about 10% of patients with Marfan syndrome have been described as having a mutation in TGF-βR2, which encodes for transforming growth factor beta-receptor type II, a controller of extracellular matrix production, interacting with fibrillin formation, some of these patients may now be classified as having Loeys–Dietz syndrome, described in 2005. Loeys–Dietz syndrome has many features similar to Marfan syndrome, including aortic aneurysm formation, but it also has other features, including craniofacial abnormalities such as hypertelorism and bifid uvula [59].

The importance of accurate diagnosis relates to the scope for management to be tailored to the exact subtype of the diagnosis, which can improve prediction of the rate of progression of aortic dilation and suggest the frequency for review. The main aim is to prevent aortic dilation progressing to lethal rupture or aortic dissection.

Management should include treatment to prevent or slow progression of aortic root dilation, such as beta-blockade, which is effective and should usually be commenced in early childhood. Other medications such as vasodilators and other antihypertensives (angiotensin II receptor inhibitors, i.e., losartan) may be used and may be synergistic or an alternative if beta-blockers are not tolerated.

Novel treatments targeting the underlying pathophysiology relating to damage of the aortic wall are also evolving. Advice should be given about avoiding activities that might cause aneurysm rupture, such as contact sport and isometric efforts involving a Valsalva maneuver, such as weight-lifting, whereas moderate aerobic activity is acceptable. Pregnancy increases the risk of aortic rupture, especially if the aortic root is already 4 cm at the beginning of the pregnancy. Repeated ophthalmic follow-up is also required for patients with Marfan syndrome. Historically, 50% of patients with Marfan syndrome died before the age of 40, whereas more recently median survival can be greater than 70 years [60].

Serial echocardiography to monitor the aortic root and also the aortic and mitral valves and the pulmonary artery should commence at diagnosis of Marfan syndrome and be at least yearly at first. Significant aortic dilation is unusual in children less than 10 years of age. Following the “z score” for aortic root dimensions is appropriate in childhood. Indications for elective surgery for aortic root dilation in older children will depend on both the degree of the dilation and the rate of increase. Dissection of the aorta due to Marfan syndrome is very rare in childhood. Associated aortic or mitral valve regurgitation is a more common indication for surgery in children. Cardiac surgical intervention for Marfan syndrome in infants and young children is usually for MR, in severely affected patients.

**Ehlers–Danlos syndrome**

Ehlers–Danlos syndrome has six subtypes. The main general features are hyperextensible skin, hypermobile joints and connective tissue fragility. Type IV is “vascular type Ehlers–Danlos syndrome.” This is an autosomal dominant condition associated with mutations in the COL3A1 gene on chromosome 2, which encodes for the collagen alpha 1 (III) chain. It has an incidence of about 1 in 5,000–20,000. About 50% of cases arise as new mutations. This variant is associated with arterial aneurysms at many locations, including the aorta. There is also an association with gastrointestinal perforation and uterine rupture in pregnancy related to vascular Ehlers–Danlos syndrome. Recognition of the syndrome before these life-threatening complications occur may allow prevention or earlier intervention.

Other examples of syndromic genetic conditions associated with aortic aneurysm formation include Noonan syndrome, Williams syndrome, autosomal dominant polycystic kidney disease, Turner syndrome, homocystinuria, osteogenesis imperfecta, and pseudoxanthoma elasticum. Conditions associated with coarctation of the aorta and hypertension may be associated with aneurysm formation due to the increased wall stress associated with the hypertension.

**Sinus of Valsalva aneurysms**

Aneurysm of a sinus of Valsalva may affect any one of the three sinuses. Dilation involving all three sinuses is classified as aneurysm of the root of the aorta, and usually relates to fusiform dilation due to connective tissue disease [61]. The sinuses of Valsalva create the aortic root, originating at the aortic annulus and terminating at the sinotubular junction, where the ascending aorta commences. Although acquired aneurysms of the sinus of Valsalva can occur due to trauma, infection or surgery, most are congenital. Aneurysm of the right sinus of Valsalva is the commonest, accounting for 60–85%, with aneurysms of the anterior, non-coronary sinus accounting for most of the rest and aneurysm of the left sinus accounting for less than 5%. There is an association (30–60%) between VSDs, which are just below the annulus fibrosus, and aneurysm of the sinus of Valsalva, where there is separation of the aortic media from the annulus fibrosus and abnormal elastin deposition, creating a weak area, which expands to create the aneurysm of the sinus of Valsalva. An aneurysm of the right sinus of Valsalva can rupture into the pulmonary artery and any chamber of the heart except the left atrium. This creates a fistula which may be sufficiently high-flow to cause acute cardiac failure. Rupture into the pericardium will cause acute pericardial tamponade. The left and anterior non-coronary sinuses of Valsalva can rupture into any cardiac chamber or the pericardium, but not the pulmonary artery when the great arteries are normally placed. The commonest fistulas are from a right sinus of Valsalva aneurysm to the right
ventricle (about two-thirds) or into the right atrium, other sites of rupture being rare. Unruptured aneurysms may be large and obstruct the right ventricular outflow tract. A coronary artery may be compressed by an aneurysm of a sinus of Valsalva. Congenital aneurysms of the sinus of Valsalva are more common in males (4:1) and in some Asian communities, where there is a stronger association (60%) with supracristal VSDs, which are more common in those communities. There is also an association with aortic regurgitation (20–30%) and bicuspid aortic valve (10%). Presentation is almost always with signs or symptoms of a complication of the aneurysm or in association with investigation of aortic regurgitation or VSD. Presentation in early childhood is very rare, but some cases present in older children and in early adult life.

**Aortopathy and aortic dilation with CHD**

Long-term follow up of many congenital abnormalities of the heart and great vessels demonstrates an increased incidence of aortic dilation, which may have a number of mechanisms [62]. Conditions that increase either flow or pressure in the proximal aorta may be associated with aortic dilation. Thus, for example, patients with systemic arterial to pulmonary shunts, truncus arteriosus, aortic incompetence, or coarctation of the aorta will be at risk. Abnormalities of the wall of the aorta may be induced by abnormal flow patterns that create shear forces, so that turbulent flow associated with aortic stenosis may induce aortic wall changes resulting in post-stenotic dilation of the aorta. There is also evidence that the aortic wall may be normal as a more general association of the underlying cardiovascular abnormality. Patients with bicuspid aortic valves are more prone to aortic dilation and dissection, even in the absence of stenosis or regurgitation of the aortic valve. The presence of genetic abnormalities such as in the gene for fibrillin, which are otherwise asymptomatic, may be associated with aortic dilation in the presence of CHD. In many situations, a number of these factors may be present. There is a significant incidence of aortic dilation in patients with tetralogy of Fallot, especially if definitive repair is delayed and also if a patient is palliated long term with a systemic-to-pulmonary shunt. It is likely that all the mechanisms described are involved with both congenital and acquired abnormalities of the aorta exacerbated by the high flow in the aorta prior to definitive repair. About half of the patients with tetralogy of Fallot with a dilated aorta have abnormalities in the fibrillin gene and patients with an abnormal fibrillin gene and tetralogy of Fallot are eight times more likely to have aortic dilation than those without the gene abnormality.

Situations where the pulmonary valve acts as the systemic valve and neo-aortic root, such as after the arterial switch operation or Ross procedures, are also associated with a significant long-term incidence of neo-aortic root dilation.

Coarctation of the aorta has multiple mechanisms for being associated with aneurysm of the aorta. The high proximal pressure will increase wall stress and may produce aneurysms of the ascending aorta. Even post-repair, residual gradients, but also abnormal flow characteristics due to the abnormal geometry of the aorta, can be associated with histological changes in the aortic wall, decreased compliance, systolic hypertension, and chronic evolution of damage to the wall and potentially left ventricular hypertrophy. The hypertension and vessel wall damage can lead to aneurysm formation. It is also possible for aneurysms to arise in the distal arch and descending aorta as local complications of the surgical repair of coarctation.

The pathophysiological consequences of these enlargements of the aorta in association with CHD are different from those seen in the connective tissue disorders. The likelihood of aortic dissection or rupture is much greater in the connective tissue disorders, such as Marfan syndrome. Dilation of the aortic root, leading to aortic regurgitation, and changes in aortic elasticity and compliance that adversely affect long-term ventricular function are more likely outcomes in patients with aortic dilation associated with CHD.

**Pathophysiology of aortic aneurysms**

The law of Laplace (wall tension is proportional to pressure \( \times \) radius) can be modified and applied to blood vessels and explains why aneurysms tend to expand and rupture. The wall tension is proportional to the pressure differential across the wall and the radius of the vessel. From these relations, it can be seen that, as a vessel dilates, the radius increases and, even with the internal pressures unchanged, the wall tension will increase, making further dilation and rupture more likely. If the pressure inside is greater, wall tension will increase and dilation and rupture are also more likely. Tissue stress can be decreased by increasing the thickness of the wall (allowing the “retaining force” to be distributed over more tissue). The dilation process will often be associated with thinning of the vessel wall, which will increase the stress on the tissue, thereby increasing the likelihood of expansion of the aneurysm. Some pathologies may be associated with changes, such as fibrosis, that will thicken the wall and change the tissue characteristics, decreasing tissue stress and potentially stabilizing an aneurysm. Usually, inexorable expansion and, eventually, more rapid dilation and rupture are the most likely outcomes, but the time frames for these processes may be very variable. Dissection of the inner layers may occur as the tissues distend or the underlying pathology progresses. In most conditions associated with aortic aneurysm, abnormalities of the aortic media develop so that loss of elastin and changes in collagen progress, with cystic degeneration and necrosis of portions of the media a common finding. If the intima splits with dilation or other pathology, the abnormal media will be especially prone to dissection.
**Surgical approaches for aortic aneurysms in children**

Most aortic aneurysms in childhood involve the root and ascending aorta. In one large series of patients having cardiac surgery for Marfan syndrome, only 11% of patients were children (under 18 years of age). Patients with Marfan syndrome having surgery early in life usually have MR as the indication. Aortic aneurysm caused by connective tissues disorder is rarely the primary indication for surgery in early childhood, although the frequency rises in later childhood [63].

The major surgical advance in aortic root replacement over the last few decades, especially for children, has been the evolution of valve-sparing aortic root replacement [64]. The historical breakthrough in aortic root replacement was the Bentall procedure, which involved aortic valve replacement, a tube replacement of the aortic root and reimplantation of the coronary arteries. This procedure had very good results and is still widely used for particular indications, especially in adults. In children, the issues of lifelong anticoagulation associated with prosthetic aortic valves, and the failure of growth and long-term complications of prosthetic valves were a particular stimulus for attempting surgery to replace the aortic root while leaving the aortic valve intact. Two major techniques were introduced and there have been many variants. “Remodeling,” introduced by Yacoub, involved a proximally scalloped aortic tube graft, which is sutured above the aortic annulus with the longer scalloped portions sewn along the line of the attachments of the aortic valves, mimicking the sinuses of Valsalva and providing some distensibility of the aortic root, which is closer to the normal physiology. This is technically a more straightforward procedure than the alternative reimplantation techniques, but still requires coronary re-implantation. The greatest medium-term risk with the remodeling technique was recurrent aortic annulus dilation and aortic regurgitation, especially in children who usually have an underlying connective tissue disorder. Various techniques to support the aortic annulus and prevent subsequent dilation and aortic regurgitation have been added to this technique to decrease that risk.

Reimplantation, introduced by David, anchored the aortic tube to the ventricular side of the aortic annulus with a second proximal suture line in a position similar to that used for the remodeling technique. The major difference in the medium term is that the aortic annulus is supported and recurrent dilation at that level and consequent aortic regurgitation should be prevented [65]. In fact, early results showed problems with interference with aortic valve function, partly due to the decrease in the aortic annulus diameter, which meant that aortic valve prolapse and poor coaptation could occur, leading to aortic regurgitation. Subsequent techniques have incorporated aortic valve surgery to tailor the valves to the new geometry and decrease the risk of regurgitation. The reimplantation technique has also evolved with more recent techniques and preformed devices focused on restoring the convex curve of the aortic root, which should better mimic the normal function of the sinuses of Valsalva in relation to aortic valve function and coronary artery flow.

Modern techniques for myocardial preservation that allow for low morbidity from the long cross-clamp times required for this often extensive reconstructive surgery of the aortic root, aortic valve, and coronary reimplantation have facilitated the advances in this area. The presence of aortic regurgitation preoperatively, common in patients with a dilated aortic root, requires isolated coronary perfusion or retrograde coronary perfusion to effectively deliver cardioplegia.

**Anesthesia for aortic aneurysm surgery**

The preoperative assessment should elucidate the extent of the lesion being repaired, as well as associated cardiovascular lesions such as aortic and mitral valve regurgitation, which commonly accompany connective tissue causes of aortic aneurysm. Review of imaging studies are crucial; all patients will have echocardiography, but MRI and CT scanning are essential to define the size and extent of the aneurysm, and the properties of any aortic dissection. The non-cardiovascular lesions that accompany the various causes of aortic aneurysm, including genetic syndromes such as Marfan syndrome and inflammatory conditions such as autoimmune or infective disorders, should be investigated. A significant percentage of pediatric cases will involve “redo” sternotomy, as associated lesions, such as MR in Marfan syndrome, which presents earlier in life than aortic aneurysm, may have already required repair. Valve-sparing procedures for aortic root replacement in young children will have a moderate rate of medium-to long-term complications, such as aortic regurgitation, that will require reoperation. Recurrent aneurysm is rare and may involve suture lines or more distal aorta with progression of underlying disease. The complex interaction of aortic valve function with the aortic root means that revision surgery for aortic regurgitation may involve the whole aortic root rather than just the valve leaflets. The usual preparation for redo surgery should be considered, such as planning for the possibility of going on CPB with peripheral cannulation before opening the chest or in an emergency fashion if required during sternotomy, with appropriate access for rapid resuscitation with blood products and heparinization for urgent bypass and external defibrillation pads in place.

Many pediatric patients undergoing aortic root surgery will be older children, in contrast to the large proportion of pediatric cardiac surgeries, which are done in the first year of life (the majority of cases in many specialized pediatric centers). These older children are often generally well and asymptomatic, having had size and rate of expansion of the aortic root monitored for many years. Careful preparation includes managing their anxiety and informing them of plans for postoperative pain control.

The cardiovascular status of the pediatric patient scheduled for aortic root replacement will usually depend on associated valve lesions. Patients with Marfan syndrome
and other connective tissue disorders are likely to have been treated with beta-blockers. Care should be taken to avoid beta-blocker withdrawal syndrome, which may complicate the postoperative course. The sympathetic overactivity associated with beta-blocker withdrawal is a particular hazard in the early postoperative phase, when catastrophic bleeding and suture line dehiscence might be induced. Maintaining beta-blockade throughout the perioperative period is a reasonable strategy. Given the possibility of a long cross-clamp, some anesthesiologists will choose to have an esmolol infusion available and use it as required rather than commit to a longer-acting agent. Angiotensin receptor blockers (e.g., losartan) are usually not given on the morning of surgery, due to the risk of hypotension in the immediate postoperative period.

Hypertension should be avoided both pre- and post-bypass. Pre-bypass, it may cause rupture of the aneurysm and post-bypass it may cause excess bleeding and dehiscence of suture lines. Patients with associated aortic and/or MR are likely to have a dilated left ventricle. Occasionally, this will be associated with poor function, which will be exacerbated by myocardial ischemia associated with the cross-clamp time. Appropriate inotropic support should be matched with strategies to minimize afterload but also to maintain an adequate coronary perfusion pressure. More commonly, patients with pre-operative regurgitant valve lesions and a dilated left ventricle with good left ventricular function will have issues of a large stroke volume after the regurgitant lesions are repaired, and avoidance of hypertension will usually require postoperative vasodilator therapy and adequate analgesia and sedation.

The association of aortic root replacement procedures with reimplantation of the coronary arteries requires careful assessment of the postoperative echocardiogram in multiple leads to diagnose ischemic complications that may arise from technical issues with the reimplantation and also air, creating temporary obstruction of the coronary arteries. Coronary artery anastomoses may also be a source of bleeding, along with the often extensive aortic suture lines, and therefore the use of an antifibrinolytic agent is usually justified in these cases.

Marfan syndrome is associated with lung abnormalities that are associated with spontaneous pneumothorax. Positive pressure ventilation may cause rupture of these lesions. The risk of iatrogenic pneumothorax should be minimized by avoiding inappropriately high ventilator pressures or volumes. A high index of suspicion for pneumothorax should be maintained if ventilator or cardiovascular problems arise.

Perioperative TEE plays a key role in aortic root replacement with aortic valve preservation. The often complex surgical plans involving detailed remodeling of the aortic annulus, the curvature of the aortic root, the size of the sinotubular junction and the position of the aortic valve leaflets in relation to these structures mean that pre-bypass review of the anatomy and post-bypass review of the repair can provide crucial information regarding the need for immediate revision of inadequate surgery. Echocardiographic review of myocardial function, coronary blood flow and the success of associated surgery, such as mitral valve repair, will also assist post-bypass management [66].

### Key Points: Anesthesia for Children with Aortic Aneurysm and Aortopathy

- Aortic aneurysms are rare in young children and most commonly affect the aortic root and the ascending aorta.
- Surgery for aneurysm of the aortic root in children most commonly involves “valve-sparing” techniques, which aim to preserve function in a native aortic valve.
- Patients with a risk of aortic dilation will usually be treated with β-adrenergic blockers and/or other antihypertensive drugs.
- Control of blood pressure is a key requirement in patients with aortic aneurysm to minimize the risk of pre-bypass rupture and early postoperative bleeding and suture line dehiscence.

### Mediastinal masses

Masses arising in the anterior mediastinum are likely to involve the great vessels and tracheobronchial tree as they expand. This can have grave consequences, as anesthesia-induced changes in the geometry of the mediastinum may produce complete occlusion of the airway or obstruction of the circulation, causing cardiac arrest. This will be the main focus of this section. Although masses arising in the posterior mediastinum can have mass effects involving the airway and a range of challenging anesthesia issues, such as catecholamine secretion (neuroblastomas) and the risk of massive hemorrhage during surgical resection, they do not appear to have the risk of catastrophic respiratory or cardiovascular obstruction that may occur with anesthesia for patients with anterior mediastinal masses, even if there is some encroachment on the trachea. This may be due to these posterior mediastinal tumors’ tendency to displace rather than encase the trachea, as occurs with anterior mediastinal masses.

### Incidence, anatomy, and natural history of mediastinal masses in children

The mediastinum lies between the pleura. The compartments within the mediastinum are defined in terms of their relationship to the pericardium as superior, anterior, middle, and posterior compartments. The middle mediastinum is essentially the pericardium and its contents. The anterior and superior compartments of the mediastinum are contiguous and not separated by any physical
anatomical barrier. Some classifications, such as in radiology, merge the anterior and superior compartments into a single anterior mediastinum. This latter classification is usually used when anterior mediastinal masses are referred to in the anesthesia literature.

From a pathological perspective, the incidence of mediastinal mass may be as low as 1 in 150,000 of the pediatric population per year. Tumors are the commonest cause of mediastinal mass. Hodgkin’s and non-Hodgkin’s lymphoma (NHL), teratomas, and germ cell tumors arising from the anterior mediastinum account for more than half of all mediastinal masses. NHL is a complex spectrum of lymphomas, including lymphoblastic lymphoma which may be the same cells as some leukemias, but with a clear local mediastinal origin. Some of these tumors will have blast cells on blood examination. The thymus and concentration of lymph nodes in the anterior mediastinal compartment explain the propensity for lymphoma to arise in this region. Neuroblastomas, ganglioneuromas, and neurofibroma, arising from the sympathetic chain and nerve roots in the posterior mediastinum, account for about a quarter of mediastinal masses. A wide variety of diagnoses of very low frequency account for the remainder. These include other tumors, inflammatory processes, congenital anomalies (such as bronchogenic cysts or esophageal duplication cysts) and, in some series, can include vascular anomalies, such as double aortic arch, which are seen as an expansion of the mediastinum on plain chest radiograph [67].

Diagnosis of anterior mediastinal masses
Clinical presentation, particularly duration of symptoms and associated features such as fever and weight loss combined with imaging and blood tests, including looking for blast cells and tumor markers, will often confirm the diagnosis or greatly narrow the diagnostic possibilities. If the mass is a tumor, tissue diagnosis will nearly always be crucial to creating a treatment plan. Many of these tumors have an excellent prognosis, but the optimum treatment protocols are very specific to the type and subclassification of the tumor.

Expert oncological advice can lead to sophisticated means of obtaining a diagnosis by relatively non-invasive methods, which may avert the need for anesthesia or allow the use of lower-risk techniques rather than general anesthesia and open surgical biopsy. The anesthesiologist’s concern about the risks of anesthesia in a patient with a mediastinal mass must be carefully integrated with the risks of all the strategies available and the clinical information about what the tumor is likely to be. There is evidence that anesthesia risk is related to the size and position of the mass as well as the anesthesia/sedation/analgesia technique used, but convincing data about the incidence of cardiovascular or respiratory disaster with anesthesia in these cases are lacking. Suggestions that patients should be treated “blindly” (without making a tissue diagnosis) with steroids, chemotherapy, or radiation due to the anesthesia risk may condemn a patient to suboptimal oncologic treatment and a potentially greater risk, which is also hard to quantify in a disease that is usually curable. An experienced pediatric oncologist will also be well placed to assess the likely clinical diagnosis on review of all the patient’s clinical information that can be gathered without anesthesia. Occasionally a younger child with a history and imaging typical of NHL and severe life-threatening airway and/or cardiovascular compression may be selected for “blind” treatment rather than risk anesthesia. “Blind therapy” is only offered after a careful analysis that the lesion is likely to respond rapidly to blind therapy, that diagnosis cannot really be made without a procedure requiring anesthesia, and that the risk of anesthesia outweighs the risks of blind therapy. The concept that biopsy can be done after blind therapy is flawed, as the lesion that is most likely to be treated blindly, NHL, is so sensitive to initial therapy that biopsy after this will often only reveal non-diagnostic necrotic tissue. Even if the tissue is diagnostic and therapy can be tailored to this, there may be a worsening prognosis if the initial therapy does not match the current recommended therapy for that tumor subgroup. Clearly, it would be catastrophic if the patient were to die from the anesthesia in an attempt to make the diagnosis. The major advance in this area has been an appreciation that with careful multidisciplinary planning, involving oncologist, anesthesiologist, and proceduralist (surgeon or interventional radiologist), to obtain the diagnosis with the most minimal intervention, only a small minority of these patients with very high-risk compression and no means of obtaining a diagnosis by relatively non-invasive means will be managed with “blind treatment.” Most of these will be young children with significant airway compression and a clinical diagnosis of probable NHL.

Planning the least invasive method for making a diagnosis should be tailored to the patient’s clinical findings. Simple venous blood sampling may contain blast cells in leukemia or tumor markers (e.g., with germ cell tumors). Pleural effusion may be easily sampled and very sensitive techniques such as polymerase chain reaction can identify specific tumor nucleic acid sequences in samples that may not have diagnostic cells on microscopy. The patient may have lymph nodes that are easily accessible for biopsy or removal with local anesthesia (potentially with sedation). Bone marrow biopsy is positive in a significant proportion of patients with NHL, but only a small minority with Hodgkin’s lymphoma. Large mediastinal masses often provide an easy target for image-guided needle biopsy that may not require formal general anesthesia. Ultrasound guidance may be adequate and can allow the procedure to be done in an operating room rather than in a CT scanner [68]. Only a small minority of patients will require a thorascopic or open procedure to sample an anterior mediastinal mass. Successful use of local anesthesia for a mediastinotomy (Chamberlain procedure) for open biopsy has been described in children as young as 8 years old.
Screening for mediastinal mass prior to anesthesia in patients being investigated for possible lymphoma in other locations in the body is a reasonable precaution. In situations where there are abnormalities such as significantly enlarged lymph nodes in other sites or atypical asymmetric or recurrent adenotonsillar masses suggestive of lymphoma, imaging of the chest should be considered prior to anesthesia. There have been complications of undiagnosed anterior mediastinal masses where a patient was having an anesthesia for biopsy of a lesion that was suspected to be lymphoma. If lymphoma is a genuine possibility, the patient may be better served by referral to a specialist pediatric oncology unit prior to biopsy, rather than doing the biopsy in an institution with less specialized services.

Pathophysiology
The anterior mediastinal compartment is very shallow inferiorly and quite crowded with the trachea and great vessels in the superior aspect. Tumors in this position are restricted by the sternum anteriorly and the pericardium posteriorly. The path of least resistance to growth is around the base of the heart and great vessels anterior to the trachea and bronchi. The tendency is to surround these structures anteriorly and laterally, before they are encased. It is important to note that it is not just the tracheal part of the airway that might be compressed and that bronchial compression, including bilateral bronchial compression, may be possible. This is of great importance, as not all cases with anterior mediastinal mass where acute airway obstruction is provoked by anesthesia will see the airway obstruction overcome with a rigid bronchoscope.

Catastrophic airway or circulatory complications have been described in case reports of patients with anterior mediastinal masses under anesthesia; however, the mechanism remains uncertain. Case series from major centers have seen respiratory complications occur in about 10–20% of cases anesthetized, but those complications have usually been relatively minor without long-term consequences. A number of centers did not anesthetize higher-risk patients [69–71].

All of these reports emphasize the ability to make the diagnosis by relatively minimal invasive techniques and the fact that local anesthesia and specially selected sedation and analgesia with spontaneous ventilation will allow most diagnostic procedures to be performed. None of the case series has a report of catastrophic airway or circulatory problem under anesthesia. In one series, there was one patient, not sedated or anesthetized, who received brief cardiac massage when their airway became obstructed on lying supine in a CT scanner. The case series data support the concept that masses creating more respiratory obstruction and symptoms are more dangerous. However, there have also been case reports of catastrophic complication in both patients with apparently low-risk masses and those receiving what should be low-risk sedation/analgesia techniques. One hypothesis for the mechanism of catastrophic obstructive complications is based on the fact that the tumor expansion flattens and holds rigid the encased (or partially encased) airways or circulatory structures, creating a ribbon-like cross-section. The well-described changes in lung mechanics at induction of standard general anesthesia include a loss of functional residual capacity based on the diaphragm moving cranially and changes in chest wall muscle tension. It is quite plausible that this change in conformity of the thorax could completely kink the flattened ribbon-like structures created by the tumor compression. This concept has informed practice in selecting techniques (avoiding anesthesia and choosing sedation techniques more likely to preserve normal lung mechanics and spontaneous ventilation) for managing these patients and may account for the absence of catastrophic obstruction in the series from major institutions.

Anesthesiologists should be aware of the extraordinary rate of expansion of some non-Hodgkin’s lymphomas. The “doubling time” (average time for a cell division cycle which will double the size of the tumor) may range from as little as 12 hours to a few days. A patient presenting with a mediastinal tumor due to NHL, perhaps having an imaging procedure without anesthesia, may have very significant disease progression and increased compression of cardiopulmonary structures 24 hours later when a procedure involving the anesthesiologist is planned. This should inform efforts to rapidly diagnose and treat these patients and review their clinical status for worsening obstructive signs or symptoms, even if they have had reassuring imaging in previous days.

Anesthesiologists should be mindful to avoid the routine use of steroids as antiemetics in these patients. Steroids may cause rapid necrosis of the tumor, which could jeopardize diagnosis, cause tumor lysis syndrome to be induced, and disturb the current best-practice protocol to cure the patient, potentially worsening prognosis. Tumor lysis syndrome is caused by rapid necrosis of the large tumor when exposed to therapeutic agents with systemic absorption of the released intracellular contents. Lethal hyperkalemia and renal failure are the most prominent complications. These patients are intensively monitored and managed for tumor lysis syndrome in oncology protocols. Steroid use in a patient with an unsuspected mediastinal mass has been associated with lethal tumor necrosis syndrome.

Surgery for anterior mediastinal masses
Open surgery for removal of an anterior mediastinal mass is rarely required in children. Occasional tumors and other lesions that cannot be managed medically may require surgery. The surgical approach will usually be by sternotomy or mediastinoscopy. Mediastinotomy or anterior thoracotomy has been used for biopsy of these lesions, and a technique for doing mediastinotomy with local anesthesia has been described. For some tumors undergoing surgical removal, the use of CPB, although
Anesthesia for patients with anterior mediastinal mass

Most procedures will be for diagnostic interventions. Preoperative assessment should include confirmation that the least invasive method for establishing an adequate diagnosis is being chosen so that anesthesia requirements will be minimized.

General assessment should be done along with specific history and examination of the patient to assess mass effects and associated conditions. History may reveal difficulties with respiration, with dyspnea and stridor, which may be intermittent. Special enquiry should be made as to whether posture affects symptoms. Some of these patients cannot tolerate lying flat, especially when supine. Facing one side or another may worsen or improve symptoms. Signs of superior vena caval compression are ominous. This may include upper body edema, often involving the face, and prominent veins with distended non-pulsatile jugular veins. The edema may be worse on waking in the morning and regress with upright posture during the day. Pemberton’s sign, which involves evoking symptoms and signs of caval obstruction when patients stretch both arms above their head, may reveal lesser degrees of obstruction.

The superior vena cava is quite posterior in the anterior mediastinal space, so caval involvement will usually reflect extensive tumor infiltration that is likely to have involved airway structures as well as vascular structures.

The postural relationship of symptoms and signs may be very important not only for planning safe postures during procedures but also for defining possible safer positions into which a patient might be moved should severe obstruction arise. The fact that arm and shoulder position may increase pressure on the superior part of the anterior mediastinum may be particularly important for positioning during CT scanning and some surgeries.

Imaging of the chest will provide crucial information. CT scanning is often the technique of choice in symptomatic children, as tolerating the duration and positioning required for an MRI while awake may be impossible. The short time required for CT imaging makes this much more practical, but not without hazard in children who have difficulty lying flat and putting their arms above their heads as is usually requested for a CT of the chest. Careful review of the CT can outline the degree and extent of compression of the airway and great vessels and heart, especially the right ventricular outflow tract. Pleural and pericardial effusions are quite common in these patients, especially those with NHL. Echocardiographic review will quantify pericardial effusion accurately and should ask for careful examination of the path of the pulmonary artery and superior vena cava and the right ventricular outflow. Standard views to confirm normal contractility and valve function are usually not relevant to these patients. Some structures may be visualized via echocardiography “windows,” which would not normally be available but are created by the presence of the tumor; these allow an experienced sonographer to obtain better views.

Widely quoted criteria for critical airway compression in children with anterior mediastinal masses that contraindicate anesthesia are: (i) a 50% reduction in predicted tracheal diameter on CT scan; (ii) a 50% reduction in peak expiratory flow rate on spirometry; (iii) severe narrowing or complete occlusion of one or both main-stem bronchi; or (iv) clinical findings of acute respiratory distress or impending respiratory failure. These points are not robustly defined but have been widely adopted. The original series that promulgated these criteria involved no patient with those criteria being anesthetized (so there is no estimate of the hazard of anesthesia in those who fulfill the criteria), and the modest number (17 in the original paper) who had anesthesia or sedation in whom there was a lack of serious complications adds to data from similar series, but an unacceptably high incidence of serious complications is likely not to be detected in a series that size. Despite this criticism of the detail of the data, the principles on which this group bases management are very sound. The practical points are that biopsies were performed using local anesthesia in most patients they deemed at high risk from anesthesia. They have since added to the series and refined an algorithm for gaining a diagnosis with the most minimally invasive procedures done first. In a latter series of 40 patients with anterior mediastinal mass who fulfilled their criteria for critical airway compression, only two of the patients had therapy without a tissue diagnosis (“blind therapy”), and, in that series, only three had general anesthesia.

Anghelescu et al.’s [70] analysis of 117 patients with a mediastinal mass who were anesthetized, with 11 having respiratory complications of anesthesia, showed that these complications were statistically associated with orthopnea, upper body edema, great vessel compression, and main-stem bronchus compression. Pleural effusion and tracheal compression did not quite reach statistical significance. This group also emphasized the importance of using minimally invasive techniques to make a diagnosis and modified anesthesia in attempt to decrease risk, avoiding muscle relaxants and maintaining spontaneous ventilation.

Overview of the literature suggests that sudden induction of deep general anesthesia in patients with an anterior mediastinal mass may unpredictably cause complete respiratory obstruction or circulatory arrest. Larger symptomatic masses with airway compression are probably at greater risk, but all patients should be treated with caution. Most patients can have their condition diagnosed with techniques that rely on local anesthesia. The patient should, where possible, be positioned in a manner...
determined preoperatively as not exacerbating symptoms. A note should be made of the patient’s most comfortable position, from a symptom point of view, as that may be incorporated into the positioning for the procedure, if possible, or used as a rescue position should difficulties arise. Apart from lateral and prone positioning, it has also been suggested that physically pulling the sternum forward may move the tumor away from the airway or heart and great vessels and may relieve acute compression.

If a patient can pragmatically have a procedure done with local anesthesia, that should be the aim. If systemic agents are required to achieve sedation and analgesia, careful titration aimed at maintaining spontaneous ventilation can avoid most incidents of catastrophic collapse. There are disturbing isolated case reports of cautious techniques still being associated with significant complications, but there are also a large number of case series with careful case selection and modified anesthesia techniques without serious complication. In association with local anesthesia, various combinations of midazolam, ketamine, and, more recently, dexmedetomidine, perhaps titrated with small boluses and maintained with an infusion, can provide a low risk of major change in conformation of the chest wall and catastrophic cardiorespiratory compression. Spontaneous ventilation and, in many cases, consciousness can be maintained while a procedure is performed. CPAP by face mask may assist with maintaining airway patency during the procedure. Endotracheal intubation is usually avoided. Topical anesthesia to the airway can facilitate intubation in cases where this is required. This may assist maintenance of spontaneous ventilation with modest anesthesia requirements. The addition of opioids if intubation is required can help with tolerance of the tube, but can increase the risk of apnea. Similarly, very low-dose infusions (e.g., 2 mg/kg/hour) with small boluses (e.g., 0.2 mg/kg) of propofol may be cautiously

![Figure 26.16](image)

**Figure 26.16** An algorithm for anesthetic management of the child with anterior mediastinal mass. CBC, complete blood count; CPB, cardiopulmonary bypass; CT, computed tomography; CXR, chest x-ray; LP, lumbar puncture; PICU, pediatric intensive care unit; SVC, superior vena cava. Tumor treatment consists of radiation or medical treatment before tissue diagnosis; considered only as a last resort after discussion with oncologist. (Source: Hammer [72]. Modified and reproduced with permission of Wiley.)
introduced for similar indications. The principle is that the minimum sedation/anesthesia necessary should be used and changes should be small and incremental. This will minimize the risk of “overshoot” in depth of anesthesia, perhaps allowing detection of deterioration before catastrophe occurs, with a good chance of rapid return to the depth of sedation/anesthesia that was previously tolerated. Most of these sedation/anesthesia strategies involve agents that produce effects that are not well monitored by proprietary depth of anesthesia monitors.

It is appropriate to have emergency equipment (and appropriately skilled staff) to try and regain the airway available. This may include a rigid bronchoscope and reinforced endotracheal tubes to overcome a compressed trachea. It is notable that some large masses may cause bilateral bronchial compression, and obstruction at that level will not be overcome by these techniques. The role of CPB is controversial. Pragmatically, if a patient suffers circulatory arrest due to compression of the heart and great vessels or complete airway obstruction, resuscitation is not likely to be adequate to prevent death or brain damage and it will take too long to initiate CPB. A realistic role would be in a case where the risk was extremely high, and the patient definitely required general anesthesia, perhaps for resection of an unusual tumor in the anterior mediastinum. Then, placing the patient on CPB or preparing appropriate vessels for cannulation with local anesthesia and perhaps minimal sedation might be reasonable before commencing anesthesia. An algorithm for anesthetic management for anterior mediastinal mass is presented in Figure 26.16 [72].

**KEY POINTS: ANESTHESIA FOR CHILDREN WITH MEDIASTINAL MASSES**

- Anterior mediastinal masses are at risk of creating lethal airway or cardiovascular compression with general anesthesia.
- Most patients will not require a standard general anesthetic.
- Local anesthesia should be combined with any sedation/analgesia/anesthesia to minimize requirements for systemic agents.
- CPB may have a role in rare cases of high-risk mass where it is initiated after preparation for cannulation is done with local anesthesia and the patient awake or receiving sedation.


CHAPTER 27

Anesthesia for Cardiac and Pulmonary Transplantation

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Heart transplantation

Over 160,000 heart and lung transplantations have been reported to the Scientific Registry of the International Society for Heart and Lung Transplantation (ISHLT) [1] since Christiaan Barnard performed the first human heart transplant on December 3, 1967 [2]. Annually, roughly 350–400 heart transplantations are performed in children in the USA. Nearly half of the centers reporting to the ISHLT perform >10 heart transplants per year. The number of reported pediatric recipients has remained relatively stable during the last decade despite improved survival, in part because of limited donor organ availability (Figure 27.1) [3]. Infancy is the commonest age for children to undergo heart transplantation (Figure 27.2).

Organ transplantation in the USA is sanctioned by congressional mandate through the Nation Organ Transplant Act (NOTA). An Organ Procurement and Transplant Network (OPTN) was created and is administered by the United Network for Organ Sharing (UNOS). UNOS has three recipient status categories for patients listed for heart transplantation: status IA, IB, and II, with status IA indicating the sickest patients who are in urgent need of transplantation for survival. Status 7 patients are those previously listed as Status IA, IB, or II, but considered temporarily unsuitable to receive a heart transplant, e.g., due to active infection.

Indications for heart transplantation

Indications for heart transplantation were recently updated [4]. Heart transplantation is generally indicated when expected survival is less than 1 or 2 years and/or when there is unacceptable quality of life secondary to irreparable cardiac diseases. As survival rates have improved, often the dilemma is no longer whether to transplant, but rather when to do it [5]. Premature transplantation results in exposure of the recipient to the hazards of transplantation and immunosuppression. Excessive delay may result in death without transplantation or the development of high-risk co-morbidities, such as pulmonary hypertension and ventricular dysfunction.
as renal and liver dysfunction, malnutrition, and elevated pulmonary vascular resistance (PVR).

Indications for heart transplantation vary with age (Table 27.1). The majority of transplantations in infants are for congenital heart disease (CHD), whereas cardiomyopathy is the leading cause in older children [3].

Cardiomyopathy

Dilated cardiomyopathies have diverse etiology, including viral myocarditis, drugs (e.g., adriamycin), abnormalities of fatty acid, amino acid, glycogen and mucopolysaccharide metabolism, mitochondria and genetic disorders, chronic arrhythmia, and coronary artery abnormality [6]. Predictors of poor outcome include a family history of cardiomyopathy, syncope, ventricular arrhythmia or near-death episode, left ventricular end-diastolic pressure greater than 25 mmHg, and left ventricular ejection fraction less than 30%.

Hypertrophic cardiomyopathies include several genotypes. Risk factors for sudden death include marked left ventricular wall thickness, family history of sudden death, and non-sustained ventricular tachycardia.

Restrictive cardiomyopathies result in diastolic dysfunction. These uncommon disorders generally have a poor prognosis and are associated with myocardial infiltrative processes, such as amyloidosis, hemochromatosis, glycogen storage disease, mucopolysaccharidosis, sarcoidosis, and endomyocardial fibrosis. Elevated PVR is often present and predicts poor outcome.
Table 27.1 Indications for heart transplantation

<table>
<thead>
<tr>
<th>Pediatric Heart Transplants: Recipient Diagnosis (2006-2012)</th>
<th>Age &lt; 1 year</th>
<th>Age 1–5 years</th>
<th>Age 6–12 years</th>
<th>Age 11–17 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital heart disease</td>
<td>54%</td>
<td>39%</td>
<td>32%</td>
<td>23%</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>41%</td>
<td>56%</td>
<td>59%</td>
<td>65%</td>
</tr>
<tr>
<td>Retransplant</td>
<td>0.4%</td>
<td>2%</td>
<td>7%</td>
<td>9%</td>
</tr>
<tr>
<td>Other</td>
<td>4%</td>
<td>3%</td>
<td>2%</td>
<td>3%</td>
</tr>
</tbody>
</table>

Source: Dipchand et al. [3]. Reproduced with permission of Elsevier.

**Congenital heart disease**
This group includes children with end-stage heart failure after surgery for single- or two-ventricle physiology and patients with complex congenital heart variants with no option of palliative surgery. The number of children undergoing transplantation for hypoplastic left heart syndrome (HLHS) has diminished greatly because survival rates after staged reconstruction now exceed 80% and the significant mortality (up to 30%) while waiting for transplantation is avoided [7].

**Other indications**
Although rare, there are children who may require cardiac transplantation for unresectable cardiac tumors and other diseases, such as Kawasaki’s syndrome [8].

**KEY POINTS: HEART TRANSPLANTATION**
- The number performed per year in the USA is limited primarily by donor organ availability.
- The commonest indication for transplantation in infants is CHD.
- The commonest indication in older children is cardiomyopathy.
- Currently, approximately 25% of recipients are bridged to transplant using mechanical circulatory support.

**Recipient evaluation**
A detailed assessment of patients is required to determine their suitability for heart transplantation (Box 27.1). Factors that must be considered include severe central nervous system, liver or kidney dysfunction, pulmonary infarction, pulmonary hypertension, morbid obesity, and some infections, malignancies, or chromosomal abnormalities. Prediction of mortality after transplantation was more accurate when multiple high-risk criteria were included in the assessment of potential recipients [9].

Assessment of cardiopulmonary function usually includes cardiac catheterization and, in many cases, magnetic resonance imaging (MRI) and computed tomography (CT) cardiac imaging for describing the vascular connections, particularly in patients previously palliated for complex heart disease. The recipient’s cardiac anatomy has to be accurately delineated, because abnormal cardiovascular anatomy influences surgical technique during harvesting and transplantation. Hemodynamic measurements are required, especially determination of PVR. Transplantation in patients with PVR > 5 Wood units/m² or a transpulmonary gradient > 15 mmHg is potentially contraindicated because it is associated with acute right heart failure and increased mortality. The upper limit of PVR associated with successful cardiac transplantation has not been established in children.

All patients with pulmonary hypertension have PVR measured at baseline conditions and during administration of oxygen, nitric oxide (NO), and/or other pulmonary vasoconstrictor therapy. When the response is marginal, repeat values after 1–2 weeks of inotropic support, afterload reduction, and pulmonary vasodilation may demonstrate improvement. Experienced institutions may accept children with PVR as high as 8–12 Wood units/m² if it is reactive. Patients whose PVR does not respond to therapy may be candidates for heterotopic heart transplantation, heart–lung, domino heart, or lung transplantation. Children with restrictive cardiomyopathy are particularly prone to marked elevation of PVR, which may contribute to the poor prognosis in these patients and make cardiac transplantation problematic. Nitric oxide appears to be a good agent to demonstrate reversibility of PVR in these patients [10].

Radionuclide angiocardiography is useful for assessing systemic ventricular dysfunction in patients with complex cardiac morphology. Endomyocardial biopsy can identify acute myocarditis and myocardial infiltrates. Pulmonary function tests may be indicated for older children with chronic lung disease. Evaluation of patients with cardiomyopathy should include a metabolic work-up, because potential etiologic factors include mitochondrial disorders, and genetic studies if indicated by phenotypic appearance or family pedigree.

Infectious disease and immune system evaluation is essential. The child’s immunization status should be updated if necessary. Tests are performed for latent infections, such as cytomegalovirus or Epstein–Barr virus, that may become clinically significant during immunosuppression. Donor matching is based on ABO typing. The candidate’s blood is also screened for antibodies against sera of random blood donors and, if reactive, a serum cross-match with the donor is performed.
In recent years because of exposure to blood products, homograft material used in surgical palliation of CHD, use of ventricular assist and mechanical support devices, and patients requiring retransplantation. Determinations of panel reactive antibody (PRA) are done to delineate a patient’s potential for sensitization to donor HLA antigens. Patients with a reaction to > 10% of antigens (either class I or II) are generally considered to be allosensitized. However, this is allosensitivity to a “random” donor; having a positive cross-match with the actual donor (HLA antibody toward donor alloantigens) at the time of transplant has been clearly demonstrated to increase the risk for poor outcome after transplant. Donor-directed HLA antibodies are associated with rejection-related mortality from cellular and antibody-mediated acute rejection and CAV. Patients with PRA > 10% pre-transplant and a positive cross-match are at high risk for graft loss from hyperacute rejection and early acute cellular rejection, which in turn increase the risk of CAV.

Allosensitized patients may be excluded from heart transplant, restricted to certain donors, or experience prolonged waiting times. Some transplant programs require a prospective negative donor-specific cross-match for patients with PRA screens > 10%. However, this approach is problematic because of the donor shortage and some patients have antibodies to many HLA antigens. Therefore, perioperative management protocols for HLA-sensitized children have been developed and include pre-treatment of sensitized patients (using treatments such as intravenous immune globulin, cyclophosphamide, mycophenolate mofetil [MMF], and rituximab), intraoperative plasma exchange, and post-transplant plasmapheresis and T- and B-cell suppression [11–15].

Heart transplantation requires long-term immunosuppression, frequent invasive procedures, and lifelong medical care. Patients have to live close to the hospital during the initial months after surgery, and temporary relocation of the family may be necessary. Prolonged periods of stressful hospitalization are likely. A stable social situation is essential for success, and psychosocial evaluation is an important aspect of the pre-transplantation process.

KEY POINTS: HEART TRANSPLANT RECIPIENT EVALUATION

- Accurate delineation of the cardiovascular anatomy is required for patients with CHD in order to plan surgical strategies for harvesting and transplantation.
- Increased PVR is associated with increased mortality after transplantation.
- The PRA test reflects a patient’s potential for sensitization to donor HLA antigens.
- PRA > 10% increases the risk of graft loss and is present in about 27% of pediatric recipients.
ABO-incompatible (ABO-I) heart transplantation

Organ allocation across blood group barriers increases the donor organ pool available for heart transplantation. Since blood group O-type recipients have both anti-A and anti-B antibodies (iso-hemagglutinins), only an O-type donor is compatible and hence they have the longest wait list. Iso-hemagglutinins are not present at birth. This fact is exploited in the ABO-I heart transplantation. The first ABO-I heart transplant was performed in 1996 [16]. The waitlist mortality in the infants decreased from 58% to 6% and survival was 80% in the first year of follow up. More recently, Henderson et al. showed that the 1-year survival and rejection following ABO-I was comparable to a group of ABO-compatible (ABO-C) infants even though ABO-I recipients were sicker at the time of transplant [17]. An international multicenter trial reported a 5-year 96% survival and freedom from retransplantation in ABO-I children, the oldest recipient being 7 years of age [18]. However, in the USA, UNOS criteria for ABO-I listing is maximum age of 2 years at the time of listing and must be status 1A or 1B and report the iso-hemagglutinin titer measured within 30 days of listing. Further, the UNOS algorithm prioritizes ABO-C transplants and hence in the USA ABO-I transplants are relatively rare. However, newer guidelines have been submitted in 2013 and are pending approval at this time.

Recipient pre-transplant management

The mean waiting period from acceptance for heart transplantation to actual surgery is currently about 3 months, but it varies with the child’s age, blood group, and list status. Approximately 20% of children with cardiomyopathy and 30% of those with end-stage CHD die waiting for a donor heart [19,20].

Aggressive medical management to achieve stabilization is required and includes supplemental oxygen, diuretics, inotropic support (e.g., dobutamine, dopamine, phosphodiesterase inhibitors), arrhythmia therapy, and mechanical ventilation. Children with chronic heart failure often receive digoxin, diuretics including spironolactone, angiotensin-converting enzyme inhibitors and β-blockade therapy (e.g., metoprolol, carvedilol). Patients with severe left ventricular dilation may need anticoagulation, preferably coumadin, to prevent the development of intracardiac thrombi and systemic embolization. Amiodarone is often chosen for treating arrhythmia. Implantable defibrillators have been effective in pediatric patients large enough for these devices. Biventricular pacing is an experimental modality to improve myocardial function.

Patients with refractory myocardial failure require mechanical circulatory support as a bridge to cardiac transplantation. Extracorporeal life support and other mechanical devices as a bridge to transplant are discussed in Chapters 31 and 32. Children with renal insufficiency requiring dialysis pre-transplant have a decreased survival following transplant [21].

Donor management

In the United States and many other countries, solid organs can be obtained for transplantation by donation after brain death (DBD) or by donation after cardiac death (DCD) [22]. DBD criteria were first established in 1968; prior to this organs were obtained from DCD, including the first heart transplant. Although DBD soon became the standard for organ procurement, scarcity of available organs led to a re-examination of DCD. During DCD, the goal is to initiate organ procurement as soon as possible after ensuring that death from cardiorespiratory arrest has truly occurred, because viability of the donor organ becomes compromised when the warm ischemic time is prolonged. A North American multidisciplinary panel concluded recently that “Death can be declared after the cessation of circulation and respiratory function for 2 minutes” [23]. Despite DCD being legal and with recipient outcomes that are favorable, ethical issues still surround DCD, and DBD currently remains the primary source of organs [24].

The age distribution of pediatric heart donors is similar to that of heart recipients [3]. Echocardiography is useful for assessment of donor heart function. Widespread malignancy or infection in the prospective donor are exclusion criteria, but cardiac resuscitation and chest trauma are not contraindications, provided the donor’s hemodynamics have been stabilized and inotropic agents are no longer needed or are at minimal doses. Usually the donor should be 80–160% of the recipient’s weight, but the upper limit may be extended for neonates or for recipients with pulmonary hypertension. Attempts to limit donor heart ischemia time are important but may be hampered by transport issues. Of over 4,000 heart transplants performed in children over a 20-year period, ischemia time beyond 3.5 hours was associated with a 30% increased risk of graft loss at 6 months after pediatric heart transplant [25]. This must be taken into consideration for high-risk transplant candidates and the benefits of waiting weighed against other recipient factors.

The anesthetic management of a pediatric organ donor is beyond the scope of this chapter [26,27].

Surgical technique

There are two methods for performing heart transplantation: orthotopic, in which the recipient heart is excised and replaced in the correct anatomical position by the donor heart; and heterotopic, in which the donor heart is placed in the right side of the chest alongside the recipient organ and anastomosed so as to allow blood flow through either or both hearts. The majority of transplants in children have been of the orthotopic type.

The orthotopic approach of Lower and Shumway [28] has been employed for many years in cases where anatomy is straightforward. This technique avoids individual systemic and pulmonary venous anastomoses but results in capacious atrial chambers, comprising donor and recipient components, which contract asynchronously. It has been suggested that atrial contribution to cardiac
output (CO) may be superior with near to total cardiac transplantation. A small cuff of left atrial tissue is left in place, incorporating all pulmonary veins, and the entire right atrium is removed. Bicaval anastomoses are then performed. This technique (Figure 27.3) [29] results in a more normal anatomical result. A meta-analysis found superiority of the bicaval technique in comparison with the biatrial procedure for early atrial pressure, perioperative mortality, tricuspid valve regurgitation, and sinus rhythm [30], although others found no difference in longer-term survival [31].

Cardiac transplantation for children with congenital malformations can be more complex technically. Deep hypothermic circulatory arrest may be employed in patients requiring extensive vascular reconstruction.

**Anesthetic management**

**Pre-cardiopulmonary bypass (CPB) period**

Children listed for heart transplantation have little or no cardiac reserve and can be extremely sensitive to the perturbations induced by anesthesia and surgery. Prior to surgery, young infants and children with uncompensated heart failure are usually already in intensive care, and may have invasive lines in situ and be on ventilator support. More stable patients may have been called in from home for the transplantation surgery and could have eaten recently. Several hours usually elapse before surgery, but therapy to modify gastric pH and volume and the application of continuous cricoid pressure during induction might be required. Communication between the transplant surgeons, anesthesiologists, operating room staff, and donor procurement team is vital in order to coordinate care and ensure graft ischemia time is minimized. At the Children’s Hospital at Stanford we hold a preoperative “huddle” attended by the heart failure and transplant teams, intensive care team, and the surgeon and anesthesiologists. At this meeting, donor and recipient specific issues are addressed, including allosensitization and the need for plasmapheresis, vascular access, immunosuppressants, including steroids, that must be administered when hemostasis is satisfactory, and the need for additional procoagulant factors such as factor VIIa or prothrombin complex if the recipient has been on anticoagulants or has had several palliative procedures. Such preparation makes for a smooth perioperative management.

The advisability of premedication and the method of anesthesia induction depend upon the patient’s age, cardiac lesion, and cardiopulmonary function. Establishing invasive hemodynamic monitoring prior to induction of anesthesia may not always be feasible and so it is imperative to institute non-invasive patient monitoring prior to the administration of medications that alter hemodynamic and/or respiratory function. Anesthesia- or surgery-induced changes in heart rate (HR), preload, afterload, or contractility may precipitate hemodynamic decompensation. Meticulous airway management is vital as hypoxia and hypercarbia aggravate PVR and...
may further depress CO. Rapid sequence induction may be poorly tolerated in patients with minimal cardiorespiratory reserve. A wide variety of anesthetic agents have been used successfully. The desirable and detrimental cardiovascular effects of anesthetic agents are reviewed in Chapter 6. In children with CHD, a fentanyl/midazolam/muscle relaxant anesthetic technique was reported to preserve cardiac index better than volatile agents, provided HR was maintained [32]. Etomidate has minimal effect on hemodynamics; propofol decreases systemic vascular resistance. Nitrous oxide has myocardial depressant and pulmonary vasoconstrictor properties and is best avoided. Ketamine supports the circulation by indirectly stimulating catecholamine release. This may be blunted in children with dilated cardiomyopathy and impaired β-agonist responses, and the drug’s direct myocardial depressive effects may then predominate. Regardless of the agent used, hypotension must be anticipated and treated promptly to preserve coronary perfusion. In patients with severely reduced function, it is our practice to monitor cardiac function using transesophageal echocardiography. Usually an apical four-chamber view suffices as a visual aide to change in function. Recent excellent reviews describe the anesthetic management of children in the operating room [33, 34].

Monitoring during surgery does not differ from that used for pediatric open-heart surgery. Some authorities avoid inserting catheters into the right internal jugular vein because the vessel will later be accessed repeatedly for endomyocardial biopsies. Transesophageal echocardiography (TEE) is useful for evaluation of heart anatomy and function, mural thrombus, intracardiac air, and early post-transplant cardiac function. When pulmonary artery (PA) pressure monitoring is indicated, many institutions prefer to place a catheter directly into the PA rather than use a PA flotation catheter. The value of antifibrinolytics for primary heart transplantation is uncertain but administration should be considered in children who have previously undergone median sternotomy.

**CPB period**

The management on CPB is similar to that in children undergoing cardiac surgery. Ultrafiltration during CPB may benefit the patient by removing excess free water, hemoconcentrating red cells and coagulation factors, and modulating the inflammatory response.

**Post-CPB period**

Issues of concern include denervated donor heart, global ischemia–reperfusion injury, elevated PVR, arrhythmia, hemostasis, and hyperacute rejection.

The transplanted heart is functionally denervated. The recipient atrial remnant remains innervated but no electrical impulses cross the suture line so the donor atrium is responsible for the patient’s HR. There are two P waves on the electrocardiogram (ECG), representing activity of the transplanted and native sinoatrial nodes. Resting HR is higher than normal because vagal tone is absent and the normal beat-to-beat variations in response to respiration are lost, as are the normal responses of the heart to alterations in body position and carotid body massage. The donor heart cannot abruptly increase HR and CO in response to stress because the baroreceptor reflex is disrupted. The attenuated HR response to stress means the anesthesiologist must be particularly vigilant to ensure the child does not become too lightly anesthetized. With the loss of the baroreceptor reflex, the patient with the denervated heart may initially show an exaggerated response to hypovolemia with a marked decrease in mean blood pressure, and then a delayed exaggerated hypertensive and tachycardia response, due to endogenous catecholamine release. The Frank–Starling (pressure–volume) relationship remains intact and compensates for hypovolemia and hypotension by increasing stroke volume secondary to an increased venous return. Therefore, it is important to maintain adequate preload, especially if vasodilators are administered. Innervation of the peripheral vasculature is preserved, and changes in peripheral vascular resistance may still occur in response to alterations in sympathetic outflow from the vasomotor center due to signals from stretch receptors in the great vessels.

Drugs such as atropine, glycopyrrolate, neostigmine, and pancuronium that act on the heart through vagal or sympathetic neuromechanisms usually will not affect HR. However, there are case reports of profound bradycardia and hypotension following glycopyrrolate–neostigmine administration [35,36]. α- and β-adrenergic receptors remain intact and inotropes such as epinephrine and isoproterenol will cause appropriate responses from the heart.

The donor organ is subjected to ischemia–reperfusion injury and patients usually require inotropic support for separation from CPB. Left ventricular diastolic dysfunction is common and characterized by a restrictive ventricular filling pattern, with a reduced preload reserve and a relatively fixed stroke volume. Sinoatrial node dysfunction is relatively common. Dopamine or isoproterenol is often selected and epicardial atrioventricular pacing can be instituted if necessary to achieve the desired HR. Temporary pacing wires are advisable. Arrhythmias are quite common in the early postoperative period, usually premature atrial or premature ventricular contractions. Compression of intrathoracic structures may be problematic during closure of sternotomy, particularly if the donor heart is relatively oversized [37].

It is important to preserve donor right ventricular function by keeping PVR normal. Catecholamine release is reduced by ensuring the patient remains adequately anesthetized. Ventilation is facilitated by muscle relaxants, and normocarbia is maintained. Elevations in central venous pressure with low or normal left atrial pressure and reduced mean arterial pressure might be related to right ventricular failure. Elevated PA pressures can be discerned by echocardiography and measured invasively. Additional measures to control PVR may be necessary, including pulmonary vasodilator therapy such as NO.
The objective is to prevent acute rejection with the patient. By the transplant team to arrive in the operating room the pre-procedure huddle and the medications are ordered institution-specific. At Stanford this is discussed during the pre-procedure huddle and the medications are ordered by the transplant team to arrive in the operating room with the patient.

Blood loss during heart transplantation can be considerable and is associated with increased morbidity and mortality. Blood products are cytomegalovirus-matched, leukoreduced, and irradiated, but coagulation management is no different from that for other open-heart surgeries in children (see Chapter 13). For infants, some centers wash packed red blood cells to reduce the potassium load. Citrate-induced hypocalcemia impairs contractility and coagulation; this may be minimized by initiating a calcium infusion (calcium chloride 10–30 mg/kg/hour). Rapid platelet transfusion may aggravate PVR.

Intraoperative immunosuppression regimens are institution-specific. At Stanford this is discussed during the pre-procedure huddle and the medications are ordered by the transplant team to arrive in the operating room with the patient.

**KEY POINTS: HEART TRANSPLANT: PERIOPERATIVE MANAGEMENT**

- Patients with end-stage heart failure often require anticoagulants and anti-arrrhythmia therapy.
- Satisfactory transplantation outcomes require excellent communication and collaboration between the multiple disciplines involved in perioperative care.
- Many transplant candidates have minimal cardiopulmonary reserve and may decompensate during anesthesia induction; 20–30% of listed children die while waiting for a donor heart.
- Postoperative morbidity is directly related to the number of blood products transfused.

**Immunosuppression**

Despite advances in immune therapy, rejection continues to be a major source of morbidity and mortality in the postoperative period. Pediatric heart transplant provides a unique immunological opportunity, because the development of the immune system extends not only into infancy, but continues throughout childhood. T-cell responses and phenotype are naive compared with adults, with decreased expression of integrins and adhesion molecules. Younger age at time of transplantation is associated with better long-term survival and lower frequency of rejection compared with older children [40]. Infants and young children (up to 5 years of age) have undergone transplantation across ABO barriers without developing clinical rejection. Proposed immune mechanisms include B-cell tolerance and accommodation (absence of humoral rejection despite expression of antigens on the graft’s vascular endothelium and the circulation of corresponding antibodies in the recipient) [41].

Immunosuppressive therapies can be categorized by their actions into: (i) broad-spectrum immunosuppressants – corticosteroids; (ii) calcineurin inhibitors – cyclosporine and tacrolimus; (iii) antiproliferative agents – MMF and azathiothre; (iv) antibodies against interleukin-2 (IL-2) – basiliximab and daclizumab; (v) target of rapamycin protein (TOR) inhibitors – sirolimus; (vi) mono- and polyclonal T-cell antibodies – OKT3, antithymocyte globulin (ATG), antilymphocyte globulin; and (vii) non-drug therapies – total lymphoid irradiation, photopheresis, and plasmapheresis.

Choice of immunosuppressives is largely guided by institutional experience and the recipient’s clinical profile, rejection history, and co-morbid associations. Typical clinical use of these agents is summarized below [42]. Be aware of the potential for drug interactions because heart transplant recipients receive many different medications.

**Induction therapy.** Induction therapy remains popular in children with most receiving ATG and an IL-2 antagonist [3]. Despite the popularity of induction therapy, no significant effect of induction therapy on survival, CAV, or incidence of rejection was seen in the pediatric population [3].

**Maintenance therapy.** The objective is to prevent acute and chronic rejection while minimizing the adverse effects of immunosuppression. All regimens involve a calcineurin inhibitor. Adjunct therapy may include an antiproliferative agent or TOR inhibitor. Often, corticosteroids are also administered, although many programs attempt to limit or avoid their long-term use.

In recent years, cyclosporine and tacrolimus have been used in a similar percentage of patients and MMF has largely replaced azathiothre use early after transplant (Figure 27.4). There is a trend to shift patients who are 5 years post-transplant from cyclosporine-based regimens to tacrolimus-based regimens [3].

**Calcineurin inhibitors**

Overall survival of transplanted patients increased from 40% to 70% after the introduction of cyclosporine (Sandimmune, Neoral) in 1982. Cyclosporin binds to cyclophilin within the cytoplasm of T cells; this complex inhibits calcineurin phosphatase, thus interfering with the transcription of key cytokines required for T-cell activation and proliferation. Microemulsified formulation of cyclosporin provides better bioavailability and lower rejection rates than the original preparation that had unpredictable absorption. Therapeutic drug monitoring is essential because the therapeutic window is narrow and other drugs influence drug levels. Cyclosporine trough levels are usually maintained in the range of 100–300 ng/mL.
Adverse effects may be dose-related and include toxicity of renal, hepatic, and neurological systems, hypertension, hyperlipidemia, hirsutism, and gingival hyperplasia.

Tacrolimus (Prograf, FK506) binds to a different cytosolic binding protein (FK-binding protein) and has been particularly effective as a rescue treatment in cases where recurrent rejection has occurred with cyclosporine. Overall patient survival does not differ between the two agents but there appears to be less rejection with tacrolimus and an improved adverse effects profile with respect to hypertension, dyslipidemia, and long-term renal function [3,43,44]. Like cyclosporine, the therapeutic window is narrow and blood levels can be affected by other medications. Trough levels are maintained in the range of 5–15 ng/mL.

### Antiproliferative agents

Antiproliferative agents such as azathioprine (Imuran) and MMF (CellCept) inhibit lymphocyte proliferation and one of these agents may be added to calcineurin inhibitor therapy. The choice of either MMF or azathioprine did not have an impact on rejection rate within the first year in the pediatric heart transplant population [3].

Azathioprine is a purine antagonist that inhibits T and B cells. Bone marrow depression is common and dosing is guided by the white blood cell count. MMF converts to mycophenolic acid, an inhibitor of purine synthesis. Lymphocytes are suppressed because they lack a salvage pathway. Absorption is variable and dosing may be guided by blood levels. Gastrointestinal side-effects rather than bone marrow depression are the usual dose-limiting factor.

### Sirolimus

Proliferation signal or mammalian TOR inhibitors, everolimus and sirolimus (rapamycin), are newer agents that provide attractive options for use in heart transplantation because they are immunosuppressive and antiproliferative. TOR inhibitors work synergistically with calcineurin inhibitors and thus permit the minimization of calcineurin inhibitors without compromising efficacy. This approach is advantageous for the majority of heart transplant recipients and might provide particular benefit in specific cases, such as patients with cardiac allograft vasculopathy, malignancies and renal dysfunction, or in patients intolerant to other immunosuppressive agents. Sirolimus may inhibit the process of CAV. Adverse effects include hyperlipidemia, wound-healing complications, and proteinuria [45].

### Corticosteroids

Corticosteroids are non-specific anti-inflammatory agents that were widely used in the pre-cyclosporine era. Nowadays, they are mainly used in combination with other immunosuppressives. Many centers try to minimize the dose and duration of corticosteroid therapy. Side-effects are myriad and include higher infection risk, diabetes mellitus, bone demineralization, and coronary artery disease. Rejection risk may increase when steroids are withdrawn.

### Rejection therapy

High-dose corticosteroid, usually methyl prednisolone, is first-line therapy for acute rejection. Recurrent moderate rejection can usually be controlled with enhanced maintenance therapy (tacrolimus, sirolimus) and corticosteroids. Other agents such as polyclonal anti-T antibodies are reserved for severe rejection that is refractory or causing hemodynamic compromise.

Chronic rejection is manifest as coronary vasculopathy. There are no proven therapies that can halt or reverse this process and re-transplantation is the most
suitable option for advanced diffuse disease. It remains controversial whether statins affect progression of allograft vasculopathy or aid in its prevention in children [46].

KEY POINTS: IMMUNOSUPPRESSION AND REJECTION

- Infants have immature immune systems and appear immune-tolerant, as evidenced by their better long-term survival and the success of ABO-I heart transplantation.
- Recipients in acute rejection represent an extremely high-risk group for general anesthesia.
- Although induction therapy is commonly employed, it does not appear to convey any survival advantage in children.
- The combination of CAV and graft failure account for the majority of deaths >1 year after transplantation.

Outcome following heart transplantation

Kaplan–Meier survival curves for patients of differing ages at transplant are shown in Figure 27.5. The youngest recipients have the longest median survival to 19.7 years, although the attrition rate is highest in the first few months [3]. Table 27.2 lists the causes of early and late (10-year) mortality from ISHLT Registry data [3].

Rejection

Rejection is defined by the Pediatric Heart Transplant Study Group as the clinical decision to intensify immunosuppression in association with either histopathology or dysfunction [47]. Four clinical types are described (Table 27.3). Hyperacute rejection is rare and manifests soon after transplantation. It is mediated by pre-formed recipient cytotoxic antibodies against donor heart antigens and often leads to intractable heart failure. On average, pediatric heart transplant recipients have two acute rejection episodes during the first 3 years after transplantation, although about one-third remains rejection-free. Acute cellular rejection is fatal in < 10% of episodes; however, it is the commonest cause of death between 30 days and 3 years after heart transplantation. Acute rejection that occurs more than 2 years after transplantation is linked to poor compliance with therapy and carries a poor long-term prognosis.

Clinical evidence of rejection ranges from no symptoms to tachycardia, tachypnea, lethargy, irritability, poor feeding, fever, hepatomegaly, new murmur, gallop rhythm, and new-onset arrhythmias. Endomyocardial biopsy remains the “gold standard” for the diagnosis of acute allograft rejection. Specimens are graded for rejection on the basis of the numbers of infiltrating lymphocytes and the presence of myocyte injury [48]. Endomyocardial biopsy is expensive, invasive, technically challenging in small children, and carries small risks of cardiac perforation and tricuspid valve damage. Further, “biopsy negative” acute graft dysfunction can occur.

The use of echocardiography as a non-invasive method of diagnosing acute rejection is unresolved. Indices of systolic and diastolic dysfunction are reportedly useful but have disadvantages [49–51].

Surveillance for late rejection is controversial. In adults, there is strong evidence that intravascular ultrasound findings at 1 year are a powerful predictor of subsequent mortality, nonfatal cardiac events, and the development of angiographic coronary disease. However, experience in children is limited. Hence regular monitoring by multiple

![Figure 27.5](image-url)
Table 27.2 Causes of early and late mortality after pediatric heart transplantation (deaths: January 2000–June 2012)

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>0–30 days (N = 290)</th>
<th>31 days–1 year (N = 320)</th>
<th>&gt;1–3 years (N = 262)</th>
<th>&gt;3 years–5 years (N = 215)</th>
<th>&gt;5 years–10 years (N = 379)</th>
<th>&gt;10 years (N = 320)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary artery vasculopathy</td>
<td>3 (1.0%)</td>
<td>14 (4.4%)</td>
<td>42 (16.0%)</td>
<td>52 (24.2%)</td>
<td>90 (23.7%)</td>
<td>84 (26.3%)</td>
</tr>
<tr>
<td>Acute rejection</td>
<td>24 (8.3%)</td>
<td>50 (15.6%)</td>
<td>51 (19.5%)</td>
<td>28 (13.0%)</td>
<td>49 (12.9%)</td>
<td>16 (5.0%)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>5 (1.6%)</td>
<td>6 (2.3%)</td>
<td>7 (3.3%)</td>
<td>3 (1.3%)</td>
<td></td>
<td>26 (8.1%)</td>
</tr>
<tr>
<td>Malignancy, other</td>
<td>4 (1.3%)</td>
<td>4 (1.5%)</td>
<td>2 (0.9%)</td>
<td>8 (2.1%)</td>
<td></td>
<td>13 (4.1%)</td>
</tr>
<tr>
<td>CMV</td>
<td>7 (2.2%)</td>
<td>1 (0.4%)</td>
<td>4 (1.6%)</td>
<td>4 (1.9%)</td>
<td>4 (1.2%)</td>
<td>6 (1.9%)</td>
</tr>
<tr>
<td>Infection, non-CMV</td>
<td>35 (12.1%)</td>
<td>41 (12.8%)</td>
<td>16 (6.1%)</td>
<td>8 (3.7%)</td>
<td>16 (4.2%)</td>
<td>23 (7.2%)</td>
</tr>
<tr>
<td>Graft failure</td>
<td>103 (35.5%)</td>
<td>59 (18.4%)</td>
<td>89 (34.0%)</td>
<td>76 (35.3%)</td>
<td>129 (34.0%)</td>
<td>98 (30.6%)</td>
</tr>
<tr>
<td>Technical</td>
<td>21 (7.2%)</td>
<td>3 (0.9%)</td>
<td>1 (0.4%)</td>
<td>1 (0.5%)</td>
<td>4 (1.1%)</td>
<td>6 (1.9%)</td>
</tr>
<tr>
<td>Other</td>
<td>22 (7.6%)</td>
<td>25 (7.8%)</td>
<td>23 (8.8%)</td>
<td>16 (7.4%)</td>
<td>26 (6.9%)</td>
<td>18 (5.6%)</td>
</tr>
<tr>
<td>Multiple organ failure</td>
<td>38 (13.1%)</td>
<td>59 (18.4%)</td>
<td>12 (4.6%)</td>
<td>9 (4.2%)</td>
<td>10 (2.6%)</td>
<td>17 (5.3%)</td>
</tr>
<tr>
<td>Renal failure</td>
<td>7 (2.2%)</td>
<td>1 (0.4%)</td>
<td>1 (0.4%)</td>
<td>1 (0.5%)</td>
<td>2 (0.5%)</td>
<td>9 (2.8%)</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>14 (4.8%)</td>
<td>31 (9.7%)</td>
<td>10 (3.8%)</td>
<td>8 (3.7%)</td>
<td>11 (2.9%)</td>
<td>7 (2.2%)</td>
</tr>
<tr>
<td>Cerebrovascular</td>
<td>30 (10.3%)</td>
<td>15 (4.7%)</td>
<td>6 (2.3%)</td>
<td>7 (3.3%)</td>
<td>8 (2.1%)</td>
<td>9 (2.8%)</td>
</tr>
</tbody>
</table>

CMV, cytomegalovirus.
Source: Dipchand et al. [3]. Reproduced with permission of Elsevier.

Table 27.3 Characteristics of cardiac rejection

<table>
<thead>
<tr>
<th>Type of rejection</th>
<th>Mechanism</th>
<th>Approximate onset after transplantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperacute</td>
<td>Preformed antibodies</td>
<td>Minutes to hours</td>
</tr>
<tr>
<td>Acute cellular</td>
<td>T-cell-mediated</td>
<td>Any time (often first 3–6 months)</td>
</tr>
<tr>
<td>Acute humoral</td>
<td>Antibodies</td>
<td>Days to weeks</td>
</tr>
<tr>
<td>Chronic (coronary artery vasculopathy)</td>
<td>Both humoral and cellular</td>
<td>After the first year</td>
</tr>
</tbody>
</table>

Source: Chan & Pearson [43]. Reproduced with permission of Lippincott, Williams & Wilkins.

Infection
Infection is a significant cause of morbidity and mortality, particularly in the first 6 months after transplantation when immunosuppression is greater [3]. The most common types of serious infection are bacterial (60%), cytomegalovirus (18%), other viral (13%), fungal (7%), and protozoal (2%) [55]. Bacterial, protozoal, and fungal infections commonly involve the respiratory tract or sternal wound. Viral infections increase the risk of graft rejection, and Epstein–Barr virus is associated with lymphoproliferative disease.

At 5-year follow-up, infant recipients had higher occurrence rates of severe and chronic infections compared with older recipients and the infections were more resistant to treatment. Additionally, the incidence of autoimmune disorders (commonly autoimmune cytopenias) was noteworthy [56].

Malignancy
Although there is an increased risk of malignancy in children after heart transplantation, the risk is extremely low. Freedom from malignancy was > 90% in 10-year survivors; almost all malignancies were lymphatic in origin. Many post-transplant lymphoproliferative disorders (PTLDs) respond to reduction in immunosuppression.

KEY POINTS: HEART TRANSPLANT: MORTALITY RISK FACTORS

- Measures of pre-transplant acuity:
  - mechanical circulatory support
  - renal dialysis
  - mechanical ventilation
- Congenital heart disease
- Re-transplantation
- Increasing body mass index
Table 27.4 Post-heart transplant morbidity. Cumulative prevalence in survivors within 10 years post-transplant (follow-ups: April 1994–June 2006)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Within 10 years (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>72.3</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>17.4</td>
</tr>
<tr>
<td>Abnormal creatinine &lt; 2.5 mg/dL</td>
<td>13.2</td>
</tr>
<tr>
<td>Creatinine &gt; 2.5 mg/dL</td>
<td>1.6</td>
</tr>
<tr>
<td>Chronic dialysis</td>
<td>1.6</td>
</tr>
<tr>
<td>Renal transplant</td>
<td>1.1</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>38.2</td>
</tr>
<tr>
<td>Diabetes</td>
<td>4.5</td>
</tr>
<tr>
<td>Coronary artery vasculopathy</td>
<td>16.7</td>
</tr>
</tbody>
</table>

Source: Boucek et al. [3]. Reproduced with permission of Elsevier.

Other complications

International Society for Heart and Lung Transplantation follow-up data on complications up to 10 years after transplantation are shown in Table 27.4. Acute renal dysfunction may occur in the immediate postoperative period, probably because of the cumulative deleterious effects of a chronic low CO, CPB, and nephrotoxic drugs such as the calcineurin inhibitors. Renal dysfunction increased from 6% at 1 year to 17% at 10 years. However, the need for renal transplant was seen in only 1% by 10 years and freedom from severe renal dysfunction was approximately 90% at 9 years [3]. Risk factors for chronic renal insufficiency included pre-transplant dialysis, hypertrophic cardiomyopathy, African-American race and previous transplant. Adjusted risk of death in those who developed chronic renal insufficiency was ninefold higher than in those who did not [57].

The percentage of recipients with hypertension increased over time to 72% at 10 years post-transplantation. The only medication significantly associated with hypertension was prednisone. Hyperlipidemia also increased steadily to 38% at 10 years after transplantation. Whether abnormal cholesterol values should be treated empirically with statins or whether target ranges for intervention should be established remains controversial. Although pravastatin or atorvastatin in pediatric heart transplant recipients has resulted in significant improvements in lipid profiles, their role in preventing or reducing CAV is unclear.

Serious gastrointestinal complications have been reported in 18% of recipients (median post-transplant follow-up was 3 years). Complications included (in order) pancreatitis, cholecystitis, recurrent abdominal infection, malignancy, and intestinal pneumatosis. Half of the patients with complications required abdominal surgery [58].

Children with CHD who required extensive reconstruction of vessels during transplantation may develop stenoses at anastomotic sites (e.g., aorta, pulmonary veins). This can usually be relieved by interventional catheterization techniques but some cases may require surgery.

Quality of life

Most pediatric recipients are rapidly rehabilitated and full-time attendance at school is achieved in almost all patients within a few months of transplantation. Approximately 50% of children do not require hospitalization in the first year after transplantation. Rejection and infection are the major causes for hospitalization. The functional status of survivors is excellent. The percentage of survivors without functional limitation was 93% at 1 year and 95% at 5 and 10 years. Less than 1% required total assistance. Preadolescent children exhibited “catch-up” growth in height and weight after transplantation. Failure of linear growth was correlated with steroid requirements [3].

Formal exercise testing reveals that maximum capacities for physical work and peak HR are only approximately two-thirds of predicted. A longitudinal assessment found low peak aerobic capacity and diastolic dysfunction [59], although perhaps less so in infants [60].

A review of cognitive and psychological outcomes after pediatric heart transplantation found that recipients generally functioned within the normal range on most measures of cognitive function [61]. About 20% experienced significant symptoms of psychological distress during the first year after transplantation [62]. Post-traumatic stress disorder seems to be relatively common in parents of pediatric heart transplant recipients [63].

Evidence indicates that children with CHD should be considered separately because they have significantly lower scores on IQ and neurodevelopmental tests when compared with a normative sample [64].

Heterotopic and heart–lung transplantation

Potential recipients with elevated fixed PVR may be eligible for heterotopic heart transplantation or heart–lung transplantation. Actuarial survival rates of 83% (1 year) and 66% (5 years) have been reported; however, experience is limited [65]. Heart–lung transplantation experience is also limited, but survival rates reported are 67% (1 year) and 41% (5 years), equivalent to those of adults. Domino heart transplant surgery (transplanting the heart of a heart–lung transplant recipient into another patient) has been employed to provide “pre-conditioned” donor hearts to infants urgently in need of heart transplantation [66].

Combined heart and liver transplantation

The incidence of congenital heart defects is approximately 24% for patients with Alagille syndrome and 15% for patients with biliary atresia. Therefore, it is not surprising that the reported incidence of CHD in children undergoing liver transplantation approximates 18% [67]. Furthermore, even palliated cardiac diseases over time can lead to liver disease [68]. For example, hepatic sinusoidal dilatation and fibrosis associated with failing Fontan physiology correlate directly with hepatic venous pressure. The odds of hepatic complications after Fontan palliation increase
with duration of follow-up. A cohort of patients followed for a median of 12 years after the Fontan procedure had abnormal liver function tests (30%), coagulopathy (50%), cirrhosis (26%) and hepatic masses (3%) [69]. A modified Model for End-stage Liver Disease (MELD) score was a good predictor of risk for cardiac mortality or transplantation in patients with Fontan circulation [70].

Pediatric patients with relatively simple cardiac defects can successfully undergo liver transplantation; Manzoni et al. reported equivalent outcomes for children with and without CHD [67,71]. The consensus remains that severe cardiac defects should be corrected prior to liver transplantation in order to avoid unacceptable transplantation mortality. Lesions of concern include significant cardiopulmonary disease, pulmonary hypertension [72], hypoxemia (PaO₂ < 50 mmHg) – either from cardiac shunt or hepatopulmonary syndrome – elevated central venous pressure (>15 mmHg), and poor CO. Successful liver transplantation outcome after bi-directional Glenn palliation for HLHS has been reported [73]. Although the first pediatric heart liver transplant was reported in 1984, this remains relatively uncommon in children [74] (Figure 27.6). Of the 2,102 thoracic multi-organ transplantations reported to the UNOS database through 2011, only 238 (12%) were in the pediatric population. Of these, 10 were heart–liver (4%) and three were heart–lung–liver (1%) [75]. Investigators from Stanford University reported a series of 3 pediatric heart–liver transplants for failed single-ventricle palliation. In each case the organs were procured and implanted en bloc. All three patients were alive at 2, 3 and 5 years post-transplant [76]. The heart is first transplanted with the patent on CPB and then the liver after CPB is terminated. Proponents of these approaches argue that the new heart is protected from the hemodynamic and metabolic derangements associated with liver implantation and reperfusion. Additionally, portal-venous decompression is unnecessary and the liver cold ischemia time is reduced [77–79].

Reliable estimation of perioperative mortality is challenging and requires separate consideration of the risks posed by hepatic and cardiac dysfunction. Important challenges include the intraoperative management and postoperative renal dysfunction and pulmonary emboli [80].

For heart–liver transplantation, overall risk and transplant listing are influenced more by cardiac status than liver status [81]. Current UNOS policy allows patients waitlisted for heart–liver to be also waitlisted for heart-only and liver-only transplantation. If a heart–liver patient is offered a heart or a liver, the additional organ from the same donor is also allocated.

There is evidence in the adult transplant literature that combined heart–liver transplantation attenuates cardiac allograft vasculopathy by decreasing the rate of plaque volume and plaque index progression, thereby providing better coronary-related clinical outcomes [82].

**Retransplantation**

Retransplantation currently accounts for less than 5% of heart transplantations [3]. Indications for retransplantation are chronic severe CAV with symptoms of ischemia...
or heart failure or asymptomatic moderate or severe left ventricular dysfunction; or chronic graft dysfunction with symptoms of progressive heart failure in the absence of active rejection. Patients with graft failure due to acute rejection with hemodynamic compromise, especially < 6 months post-transplant, are regarded as inappropriate for retransplantation [83].

**Anesthetic management of children who have undergone heart transplantation**

Patients may present for surgery because of complications from cardiac transplantation (e.g., infection, malignancy, drug adverse effects), or the indication for surgery may be unrelated to heart transplantation. Successful anesthetic management requires consideration of the patient’s medical status, the physiology of the transplanted heart, and the implications of immunotherapy. These have been discussed earlier.

**Future prospects**

Donor shortage remains a frustrating problem and is the primary limitation to the number of transplants performed. Efforts to further the care of children with end-stage cardiac disease can be broadly categorized as described in the following sections.

**Alternative therapeutic modalities**

Mechanical assist devices are available for children but most are only appropriate for larger, older patients. Research continues on the development small, implantable ventricular assist devices suitable as destination therapy or as a bridge to recovery for children of all ages [84]. Another avenue of intensive research is cell-based engineering to replace damaged or dysmorphic heart tissue [85]. In animal models, intravenous injections of bone marrow–derived mesenchymal stem cells readily express phenotypic characteristics of cardiac myocytes, localize at sites of myocardial injury, prevent tissue remodeling, and improve cardiac recovery. When provided with a scaffold such as a prefabricated matrix or decellularized heart tissue, stem cells are able to localize, differentiate, and function [86]. Heart muscle patches, heart valves, and perhaps the entire heart may in the future be engineered in the laboratory [87]. Xenotransplantation also has potential [88].

**Improving current therapeutic modalities**

Opportunities abound for further refinement of existing therapies. These include re-examination of the allocation of donor organs, ethical analysis of the practice of retransplantation (which is associated with poorer outcome) [89], extended donor organ criteria, better protocols for highly sensitized patients, improved understanding of the timing of interventions such as mechanical ventricular assist (balancing the risks of intervention against the benefit of preserved end-organ function), miniaturization of pediatric CPB circuits, efforts to reduce the side-effects of immunosuppression and increase immunotolerance, better therapies to diminish the likelihood of acute and chronic rejection, and improved patient/family support and transitions to enhance compliance with care [90].

**Pediatric lung transplantation**

Lung transplantation surgery has been offered as a life saving and life extending treatment for both adults and children with irreversible end-stage lung disease. Compared to adults, the experience with pediatric lung transplantation has been modest. Since 2007, the number of centers performing pediatric lung transplant surgery and the number of transplant surgeries performed has remained relatively constant. However, since the inception of pediatric lung transplant programs in 1989, more than 2,500 pediatric lung transplant and heart–lung transplant surgeries have been reported to the Registry for the ISHLT (Figure 27.7) [91]. The outcomes of pediatric lung transplantation, although comparable to adults, remain worse than other solid organ transplant surgeries [91, 92]. Many challenges, such as a wide variety of medical conditions, donor–recipient match, and development and growth of the transplanted organs, are unique for lung transplant surgery in pediatric patients.

These children undergo multiple surgical and diagnostic interventions and frequently require sedation or general anesthesia. Thus it is vital for the anesthetic team to be familiar with the issues related to various pediatric pulmonary diseases, conduct of lung transplant surgery, and long-term consequences from the lung transplant surgery.

**Indications, contraindications, and listing criteria in children**

Generally, lung transplant surgery can be considered for any end-stage lung disease; cystic fibrosis (CF) remains the most common indication. The majority of pediatric lung transplant recipients are between the ages of 11 and 17 years of age and only 20% of total transplants are performed on children between 6 and 11 years of age. Only a few centers offer lung transplant surgery to infants and neonates for a variety of congenital and acquired cardiopulmonary lesions that result in end-stage pulmonary failure. This group accounts for approximately 10% of the total lung transplant surgeries (Table 27.5).

**Cystic fibrosis**

Cystic fibrosis remains the most common indication for the pediatric lung transplantation. CF disease, caused by a mutation in CF transmembrane conductance regulator (CFTR) protein of chloride and sodium channels, affects the pulmonary and gastrointestinal systems. Respiratory failure is the most common cause of death in these children. In the last two decades, aggressive chronic medical treatment aimed at prevention of acute exacerbations, along with improved airway clearance techniques, have improved life expectancy for children diagnosed with CF. Like their adult counterparts, lung transplantation is the final therapeutic option for these patients. Though the
ideal time to listing for a transplant remains debatable, variables such as rate of decline in forced expiratory volume in 1 second (FEV₁), elevated PaCO₂ (>50mmHg), decreasing PaO₂ (<55mmHg), deteriorating nutritional status, frequency of hospitalizations, decreasing distance on the 6-minute walk test, and family dynamics are considered prior to listing the patient for lung transplant [93,94]. In a recent review of CF patients, need for pre-transplant mechanical ventilation was a predictor of poor 1-year survival after lung transplantation [95]. Many of these children have significant co-morbidities from CF, such as diabetes, severe malnourishment, and osteoporosis. Additional surgeries for ailments such as sinusitis, nasal polyps, poor nutritional status, and meconium ileus are often needed in the preoperative period. As a result of disease progression and repeated prolonged exposure to antibiotics, these children are frequently colonized and infected with pan-resistant pathogenic organisms such as Pseudomonas aeruginosa. Certain bacteria such as Burkholderia cenocepacia are associated with higher postoperative mortality and are considered an absolute contraindication by most centers performing lung transplant surgeries [93]. Chronic antibiotic therapy often results in renal complications such as renal tubular damage and electrolyte disturbances. Hypomagnesemia and hyperkalemia are common electrolyte disturbances in these patients.

Approximately 10% of CF patients have associated liver and pancreatic disease. The malabsorption of oral medications decreases the efficacy of many drugs commonly prescribed in the perioperative period. Malnutrition associated with CF liver disease and malabsorption may be a predictor of poor outcomes, and aggressive efforts, such as placement of gastrostomy tube or parenteral nutrition aimed at improving weight and bone density, are needed while listing the patient for the transplant surgery. Preoperative diabetes requiring insulin therapy has been
shown to slightly increase relative risk of mortality in adult transplant recipients, but its effect in pediatric patients is unclear.

**Pulmonary hypertension**
Pulmonary hypertension is the second most common indication for lung transplantation in children. In children aged 6–17 years, idiopathic pulmonary hypertension accounts for about 7–8% of lung transplant surgeries. However, in younger children and infants, idiopathic or pulmonary hypertension secondary to a number of congenital or acquired etiologies is probably the commonest reason for transplant. In recent years, the medical treatment of pulmonary arterial hypertension has improved significantly, with drugs like endothelin receptor antagonists (bosentan), phosphodiesterase inhibitors (sildenafil), prostacyclin and its analogs. These drugs have been shown to reduce the pulmonary arterial pressure and reverse the histological changes in the pulmonary vascular architecture secondary to the long-standing pulmonary hypertension. The full impact of these drugs on the models used to predict the life expectancy in patients with pulmonary hypertension is yet to be completely evaluated. For children who develop irreversible pulmonary hypertension secondary to congenital cardiac defects, the decision to transplant the lung alone vs. a heart–lung transplant can be a difficult one and is usually guided by the complexity of cardiac lesion. Pulmonary hypertension resulting from veno-occlusive diseases such as pulmonary vein stenosis or alveolar-capillary dysplasia, is usually unresponsive to medical therapy, thus requiring lung transplant surgery early in life.

**Miscellaneous disorders**
Lung transplant surgery has also been performed in children for a variety of end-stage pulmonary diseases, including bronchopulmonary dysplasia, congenital diaphragmatic hernia, hemosiderosis, bronchiolitis obliterans, and pulmonary dysmaturity.

**Neonatal and infant lung transplant indications**
According to the 2013 report of the ISHLT registry, approximately 100 heart or heart–lung transplants have been performed on children younger than 1 year of age [91]. In addition to pulmonary hypertension and congenital cardiac defects, congenital disorders leading to abnormal production of surfactant is a common reason to transplant. Various genetic mutations such as surfactant protein B or protein C deficiency cause abnormal surfactant formation. These children present immediately after birth with severe respiratory failure and require significant ventilatory support or ECMO support.

**Lung transplant listing criteria**
The criteria for listing children for lung transplant surgery are based on the natural history of the disease, functional status, and expected improvement in the quality of life. Generally, a clear diagnosis with a life expectancy of less than 2 years is necessary for listing the child for the lung transplant. However, it is difficult to develop survival models for the relatively rare diseases.

Active malignancy, sepsis, tuberculosis, neuromuscular disease, multiple organ failure, and acquired immunodeficiency syndrome (AIDS) are considered as absolute contraindications for any transplant surgery. A compromised left ventricular function is also considered as an absolute contraindication in some centers. Most patients with pulmonary hypertension will have severe right ventricular dysfunction at the time of surgery, but recovery is the norm after transplant surgery. Liver disease secondary to CF is not an absolute contraindication for lung transplant. Some of these patients have been listed for combined liver–lung transplant surgery and have done unexpectedly well with good survival rates. Other factors that influence the decision to list the child for transplant surgery are history of non-compliance with medical treatment, severe uncontrolled diabetes, and severe osteoporosis.

**KEY POINTS: INDICATIONS, CONTRAINDICATIONS, AND LISTING CRITERIA**
- Cystic fibrosis is the most common indication, accounting for > 50% of pediatric lung transplants.
- Pulmonary hypertension is the second most frequent indication.
- Neonatal and infant lung transplants are uncommon; causes in this age group include congenital cardiac defects, pulmonary hypertension, and genetic surfactant protein defects.
- Life expectancy < 2 years is a criterion for lung transplant; active malignancy, sepsis, multi-organ failure, neuromuscular disease, and AIDS are contraindications.

**Donor management and lung preservation**
As with other organ transplant surgeries, donor availability has been a limiting factor in offering lung transplant surgery to larger number of patients. Only about 15–30% of the cadaveric donors lungs are considered acceptable for transplantation [93,94]. In compliance with the final rule, the OPTN implemented a new lung allocation system in 2005. This system uses medical urgency as the primary determinant of organ allocation and discouraged the use of waiting time. Under this system, a lung allocation score (LAS) is calculated for every patient > 12 years old. Multiple variables such as age, functional status, forced vital capacity (FVC), and oxygen requirement are used in calculating the LAS. The new policy also mandates that the
donor lungs from pediatric donors be preferentially given to pediatric patients [96]. Since its implementation, there has been a reduction in total number of listed patients, median time to transplant, and waiting list mortality without affecting survival after the surgery [94]. Children younger than 12 years of age still receive organs based on the waiting time accrued on the transplant list.

Donor lungs are selected after thorough medical screening and multiple laboratory tests. In younger children, comparable age and height (<20% discrepancy) are considered acceptable for matching lung volume. An ideal donor is younger than 55 years, a non-smoker, and has no history of cardiopulmonary or significant neurological disease. The donor lungs should produce good gas exchange (\(\text{PaO}_2 > 350\text{mmHg with FiO}_2\text{ of 1.0}\)) on a moderate amount of ventilatory support. The chest radiograph and bronchoscopy should rule out any significant infection, consolidation, or tumor. Ideally, the donor lungs are accepted only if the ischemic time is expected to be less than 6 hours. Over the last decade, selection criteria for ideal donor lungs have been relaxed [97–99]. Donors with mild lung pathology that is considered to be reversible with aggressive therapy fall into this category. Many biochemical markers in the bronchoalveolar lavage fluid from the donor lungs, e.g., IL-8, IL-6 and IL-1β, are being evaluated as predictors of early and late graft dysfunction. The pool of donors is not limited to brain-dead donors. In the current era, using donation after cardiac death lungs accounts for approximately 20% of donated organs. Patient survival after transplanting lungs donated after cardiac death and other marginal donors has not been compromised [97]. Recently, normothermic \textit{ex vivo} lung perfusion techniques are being evaluated to increase the number of suitable grafts. This technique maintains normal physiological status and allows cells to stay metabolically active, thus prolonging the window for transplantation [100].

Efforts to preserve lung function after the determination of death may reduce the incidence of primary graft failure and improve long-term graft function. Ventilation with tidal volumes of 6–8 mL/kg along with aggressive hemodynamic management while restricting fluid to maintain central venous pressures of 4–6 mm has been shown to optimize pulmonary function of the donor lungs [97].

The process of harvest includes systemic heparinization of the donor and infusion of prostaglandin E\(_1\) into the main PA. A number of preservation solutions have been tried but currently the Euro-Collins solution is used by most centers. Lungs are inflated with FiO\(_2\) < 0.4 to an airway pressure less than 20 cmH\(_2\)O. Lungs are removed \textit{en bloc} with descending aorta, left atrial cuff, main PA, and thoracic aorta.

Bridge to transplantation
A small number of children, especially neonates and infants, deteriorate prior to matched donor lungs becoming available. In addition to ventilator support, some children require use of ECMO to maintain oxygen and carbon dioxide exchange. However, post-transplant results of children on ECMO support at the time of transplant surgery have been poor. Recently, learning from adult experience, a small number of neonates and infants have been successfully bridged to transplant with the use of a paracorporeal Novalung Surgical Lung Assist Device (Novalung GmbH, Germany) oxygenator or the Quadrox-iD Pediatric oxygenator (MAQUET GmbH & Co KG, Germany) (Figure 27.8). This requires central placement of cannula with PA blood flow redirected to left atrium. Preliminary experience suggests that with improvements in anticoagulation therapy, use of extracorporeal lung assist devices may be expanded to support respiratory decompensation for a prolonged period [101].

**KEY POINTS: DONOR MANAGEMENT, LUNG PRESERVATION, AND BRIDGE TO TRANSPLANT**

- Only 15–30% of donor lungs are considered acceptable; the new LAS based on medical urgency is calculated for every patient > 12 years of age.
- Children < 12 years of age receive organs based on waiting time on the list
- Acceptable gas exchange, “clear” bronchoscopy and chest radiograph, and anticipated ischemic time < 6 hours are the usual criteria for donor lungs.
- ECMO or paracorporeal lung assist devices can be used as a bridge to transplant in critically ill patients.

Anesthetic management and surgical approach
After listing for lung transplantation, most children will be evaluated in the pre-anesthesia clinic and undergo extensive evaluation, including ECG, echocardiogram, pulmonary function tests, arterial blood gases, and
complete metabolic panel. Children with pre-transplant diagnosis of pulmonary hypertension also undergo a diagnostic cardiac catheterization where the response of the pulmonary vascular bed to oxygen and nitric oxide is noted and cardiac anatomy is defined.

At the time of surgery, these patients are in various degrees of end-stage lung disease. A large number of children are living at home with minimal oxygen supplementation. At the other end of the spectrum are neonates and infants, who are usually critically ill at the time of surgery. Almost all the neonates and infants who received lung transplant surgery at our institution were on chronic ventilatory or extracorporeal hemodynamic support prior to their surgery.

Like other solid organ transplants, time of surgery is unpredictable. Anesthesiologists are expected to prepare these critically ill patients for surgery in a relatively short time. Most children carry a hospital-issued pager and have been anticipating the surgery for a long period of time. They are often excited and frightened at the same time. Anxiolytics such as midazolam can be safely given to most children. One must be careful in administering sedatives to children with severe pulmonary hypertension in the absence of proper monitoring.

Standard nil per os (NPO) guidelines are followed to minimize the risk of aspiration and contamination of the new lungs. The choice of induction agent and muscle relaxant is largely guided by the patient’s condition and hemodynamics. Propofol and etomidate are safe in children with CF and other hemodynamically stable patients, but ketamine may be the preferred drug for inducing children with high pulmonary pressures. Ketamine has been shown to have a minimal effect on PVR in children. Anesthetic depth is maintained with opioids and benzodiazepines and is supplemented with inhalational agents.

Airway management normally includes the placement of a cuffed endotracheal tube. Some patients have a tracheostomy, and discussion of airway management technique with the surgeon is important. It may be necessary to intubate the trachea translaryngeally, and remove the tracheostomy temporarily during the surgery to facilitate access to the airway. The tracheal stoma may need to be occluded by suturing or adhesive dressing. The tracheostomy can be replaced soon after the surgery; most patients will not be able to be decannulated in the early postoperative period.

The anesthesiologist must ensure that the non-anesthetic drugs such as immunosuppressants and preoperative antibiotics are delivered on time. For children with pulmonary hypertension, selective vasodilators such as inhaled nitric oxide and prostacyclins must be maintained throughout the pre-bypass period to avoid rebound pulmonary hypertension.

Most often, pediatric lung transplants are performed with the assistance of CPB, and lung isolation is not required. The extensive nature of the surgery and the use of CPB mandate the need for invasive monitoring with arterial and central venous catheters. At our institution, continuous monitoring of pulmonary pressure with PA catheters is limited to adolescents with the pre-transplant diagnosis of pulmonary hypertension. A 7 Fr sheath is placed preoperatively and the catheter is advanced to the PA after the patient has been weaned from bypass. When continuous monitoring of PA pressures is indicated in smaller children, a catheter can be placed directly into the PA by the surgeon. Lung transplant surgery is a class I indication for performing intraoperative TEE, which is used to monitor the right ventricular pressures and ventricular function and to rule out pulmonary venous obstruction in the post-bypass period.

The surgery is performed through a trans-sternal, clamshell incision. A meticulous dissection is carried out to ensure the adequate exposure prior to the initiation of CPB. Adhesions in the thoracic cavity from infections and previous surgeries can cause substantial bleeding. Antifibrinolytic drugs such as tranexamic acid help in reducing bleeding. Providing adequate ventilation and oxygenation during the pre-bypass period is a challenge that the anesthesia team has to deal with. Frequent suctioning of copious secretion is needed to effectively ventilate CF patients. Many children with end-stage lung disease are chronic CO2 retainers. Ventilation during the pre-bypass period should be adjusted to maintain normal pH levels. Overzealous correction of hypercarbia often results in severe respiratory alkalosis, leading to reduced cerebral blood flow, and potentially cerebral ischemia.

**Use of CPB**

Use of CPB is an issue of much debate in adult lung transplant surgery. There are several factors that make the use of CPB necessary for the lung transplant surgery in children. CPB allows the resection of both diseased lungs simultaneously, thus minimizing the risk of cross-contamination of the new lungs. Many of these children are physically too small to accommodate even the smallest double-lumen endotracheal tube. Other children such as those with significant pulmonary hypertension and neonates are often too tenuous to tolerate single lung ventilation for any length of time. In addition, use of CPB provides stable hemodynamics during the extensive surgical dissection, greatly simplifies the anesthetic and surgical management, and consequently reduces lung ischemic times.

Use of CPB, however, comes with its own risks. Generation of inflammatory mediators and activation of complement cascade during CPB contribute to ischemic–reperfusion injury to the implanted lungs. Data from adult patients suggest that there is a higher incidence of graft dysfunction associated with the use of CPB. This observation, however, may reflect the fact that in the adult patients, CPB is more frequently used in patients with pulmonary hypertension, a pre-transplant diagnosis independently associated with worse outcome.

**Surgical technique**

During CPB, the patient is cooled to 32°C and surgery is performed without arresting the heart. Use of aortic
cross-clamping is necessary when the surgery involves a simultaneous correction of a coexisting intracardiac defect. After establishing CPB, both lungs are removed by ligating and dividing pulmonary arterial, pulmonary venous, and bronchial connections. In most recipients, the tracheobronchial tree is usually colonized with multi-antibiotic-resistant bacteria. In order to reduce the bacterial load on the new lungs, the tracheal stump of the recipient is irrigated with a concentrated solution of antibiotics such as tobramycin. While the pneumonectomies are being performed, a second surgical team simultaneously prepares the donor lungs. The implantation of the new lungs is initiated with the end-to-end bronchial anastomosis. As bronchial blood supply is compromised during the procedure, peri-bronchial tissue is wrapped around the anastomotic site to enhance healing. Vascular supply to the new lungs is established by anastomosing the donor PA to the native main PA. The pulmonary veins are reconnected to the recipient’s left atrium en bloc, using the donor’s atrial cuff. This method not only reduces the surgical time but also minimizes the risk of developing pulmonary vein stenosis. Many programs will perform a flexible fiberoptic bronchoscopy before weaning from CPB to inspect the anastomotic sites, and suction significant clots or mucus plugs.

Before weaning off the bypass machine, ventilation is resumed. Ventilator parameters are guided by the donor weight. Careful adjustments to tidal volume and airway pressures are made so that all atelectatic areas are expanded but not over-distended. Volutrauma caused by over-distension of the new lungs can increase endothelial permeability and potentiate primary graft dysfunction. If areas of atelectasis persist, flexible bronchoscopy should be performed to rule out obstruction of the bronchial anastomosis. FiO₂ should be limited to 0.4–0.5 when possible to limit oxygen toxicity; SpO₂ in the 90–95% range is often acceptable. Inhaled NO at 10–20ppm is often used to improve pulmonary arteriolar vasodilation and ventilation–perfusion mismatch. An in-depth intraoperative TEE exam is done to evaluate right ventricular function, and right ventricular pressure is estimated. Blood flow should be assessed in the PA distal to the anastomosis and in the pulmonary veins. Inotropic support and selective pulmonary vasodilator therapy with nitric oxide is initiated when high right-sided pressures are measured along with significant right ventricular dysfunction. Because of the lack of lymphatic drainage and frequent capillary leak syndrome, intravascular fluid administration should be limited, maintaining CVP in the 4–6 mmHg range. Bleeding can be problematic, especially in patients with pleural adhesions from previous surgery. After protamine and addressing surgical bleeding areas, platelets may be required, although they should be given only when absolutely necessary due to the inflammatory and vasoactive effects of platelet activation.

Many pre-transplant factors such as younger age, nutritional status, and rejection influence the need for postoperative ventilation. After initial perfusion scan and diagnostic bronchial biopsies have been performed, most children can be extubated within a few hours of the surgery. Infants and neonates tend to have a more protracted course with prolonged ventilatory needs when compared with the older children with CF (average 24 vs. 3 days) [102]. This difference can be explained by their poor preoperative status, frequent airway complications, and associated cardiac anomalies. Postoperative pain relief is usually accomplished by patient-controlled analgesics and narcotic infusions. Regional anesthesia with epidural catheter has frequently been used in adults and older children who do not require systemic heparinization. Epidural catheters can also be placed in the postoperative periods once coagulation parameters have normalized.

### KEY POINTS: ANESTHETIC MANAGEMENT AND SURGICAL APPROACH

- The preoperative condition ranges from stable at home, to chronic ventilation with tracheostomy, to mechanical support on a bridge to transplant device.
- CPB and the bilateral sequential lung transplant techniques are used for essentially every pediatric lung transplant.
- Ventilation parameters after CPB include limiting inflation pressures and volumes (chosen for the donor lungs), limiting FiO₂ to maintain SpO₂ at 90–95%, and addition of inhaled nitric oxide.

### Primary graft failure

Primary graft dysfunction (PGD) of transplanted lungs is a syndrome of acute lung injury that presents within 72 hours after transplant surgery. In its most severe form, it presents clinically as pulmonary edema with persistent, severe hypoxemia after weaning from CPB. Other reversible causes of hypoxemia, such as inadequate ventilation and right ventricular dysfunction with right-to-left shunt, must be ruled out first before the diagnosis of PGD is made.

Since 2004, ISHLT has implemented a common system grading the severity of the reperfusion injury. This system is based on PaO₂/FiO₂ ratio and chest radiograph findings (see Table 27.6) [103,104]. However, further refinements to this classification have been recently suggested. The incidence of graft dysfunction remains approximately 30%. PGD remains a major contributing factor to early and possibly delayed mortality after pediatric lung transplantation.

Vascular endothelium makes up a vast portion of the lung parenchyma. Unlike other organ transplants, oxygen is readily available to the metabolically active endothelium immediately after the onset of ischemic period. This allows production of free radicals during the ischemic period itself, making lungs more susceptible to graft failure than other solid organs. The time course of this complication
Table 27.6  International Society for Heart and Lung Transplantation recommendations for grading of primary graft dysfunction

<table>
<thead>
<tr>
<th>Grade</th>
<th>PaO₂/FiO₂ ratio</th>
<th>Radiological infiltrates consistent with pulmonary edema</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&gt;300</td>
<td>–</td>
</tr>
<tr>
<td>1</td>
<td>&gt;300</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>200–300</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>&lt;200</td>
<td>+</td>
</tr>
</tbody>
</table>

Source: Benden [91]. Reproduced with permission of Elsevier.

suggests two distinct but complementary mechanisms. The first phase, seen immediately after the reperfusion, is initiated by the donor macrophage-induced release of superoxide anions, inflammatory cytokines, mast cell degranulation, and complement activation. This is the rationale for administering the lowest FiO₂ that will maintain SpO₂ at 90–95% after CPB. All these humoral and cellular mediators damage the integrity of the vascular endothelium, causing movement of fluid to the interstitial and alveolar space. Clinically, this presents as progressive hypoxemia with copious, pink frothy secretions that are not amenable to the conventional treatment methods such as diuresis and institution of positive end-expiratory pressure (PEEP). The initial release of inflammatory cytokine induces the recruitment of the recipient’s neutrophils to the injury site within a few hours after initial injury and starts the delayed phase of PGD. During the delayed phase, neutrophils produce reactive superoxide anions and hydroxyl ions and greatly amplify the initial injury, causing further damage to the pulmonary endothelium. Neutrophils also produce elastase and block the blood flow in the capillaries, resulting in the architectural damage to the lung tissue [105,106].

Data from the adult patients have linked multiple donor factors to the genesis of PGD. These factors included female gender, African-American race, age (<21 or >45 years) and history of smoking. Amongst intraoperative factors, ischemic time longer than 6 hours was the most important factor associated with the development of PGD and higher early mortality rates. Many preventive measures have been employed to reduce the incidence of PGD. These measures include prophylactic use of prostaglandins and preservation solutions like Euro-Collins and low-potassium dextran. Other empirical measures, such as retrograde perfusion, avoidance of barotrauma, and use of surfactant, are also helpful in reducing the incidence of PGD.

Primary graft dysfunction is associated with a protracted postoperative course and significantly higher early mortality. A retrospective study that included adult and pediatric patients reported significantly higher overall mortality in patients who developed primary graft failure (28.8% vs. 4.2%) [107]. PGD has been independently correlated with bronchiolitis obliterans [107]. Huddleston et al. noticed that the incidence of bronchiolitis obliterans is lower in children who received lungs with shorter ischemic time [102].

Once PGD develops, patients are managed with aggressive cardiopulmonary support involving mechanical ventilation, inotropes and occasionally with the use of ECMO. Veno-venous ECMO is normally sufficient to improve oxygenation and CO removal and to allow minimum ventilation for lung rest. Early use of nitric oxide tends to reduce the early mortality. In most patients, PGD resolves over several days. Children who need ECMO support are expected to have significantly higher mortality.

The preventive strategies to reduce the incidence of PGD are mainly focused on improving lung preservation techniques, reducing ischemic time, improving donor management, and minimizing barotrauma. Surgeons routinely allow ejection of a small amount of blood into the PA immediately after establishing the vascular supply to the first lung. Empirical evidence suggests that the prophylactic use of pulmonary vasodilators like PGE₁ and prostacyclin may reduce the incidence and severity of the reperfusion injury. The prophylactic role of NO, however, is less clear. There have been few randomized clinical trials and they have failed to demonstrate efficacy of prophylactic administration of inhaled NO in preventing primary graft failure.

**Physiological changes and growth of the transplanted lungs**

Denervation of lungs is a consequence of the transplant surgery, but this produces few clinically significant effects on airway reflexes, mucociliary movement, and bronchial hyper-reactivity [108]. The lack of afferent stimuli to the respiratory center in transplanted patients results in poor coordination between thoracic and abdominal muscles – a frequently observed finding in the immediate postoperative period. Adult lung transplant patients show a subnormal increase in minute ventilation with carbon dioxide challenge [109]. Loss of lymphatic drainage makes the transplanted lungs more susceptible to interstitial edema, increased water content, and lower compliance [110].

Serial pulmonary function tests, radiological findings, histological evidence, and clinical examination suggest that donor lungs from younger infants and neonates continue to grow after the surgery. This growth occurs in both lung parenchyma and the larger airway and it mirrors the somatic growth of the recipient. Cohen et al. observed that functional reserve capacity increases along with somatic growth [111]. This increase accompanies a similar increase in the FEV₁, suggesting that the growth in the lungs results from an increase in the number of alveoli and not from mere distension of existing alveoli. The lobar lungs transplanted from mature, living related donors also demonstrate a similar growth pattern. However, morphometric studies suggest that the number of alveoli in these lobar lungs remains constant and the observed
growth in lung volume results primarily from alveolar distension [112]. The measurement of diffusing capacity for carbon monoxide (DLCO) provides an estimate of gas exchange surface area. Serial measurements of DLCO support the opinion that the increase in lung volume seen after mature lobes is secondary to hyperinflation.

**Surveillance**
These children are closely monitored for rejection, infection, growth, and bronchiolitis obliterans. Pulmonary function tests, bronchopulmonary lavage, and transbronchial biopsies are performed at frequent intervals. Older children can cooperate to perform spirometric tests and the values of FEV₁, FVC and flow–volume loops can be serially measured with reasonable accuracy. After the transplant surgery, most children show immediate improvement in their pulmonary function tests (see Figure 27.9). In infants and younger children (less than 2 years of age), serial values of peak expiratory flow rates are measured at different values of FRC. Peak expiratory flow rate is measured by rapid inflation, followed by a rapid deflation. This is achieved by using mask inflation followed by a rapid external thoraco-abdominal compression. These tests are non-invasive but are physically stimulating and are adversely affected by active patient resistance. Consequently, most of the children require deep sedation and/or general anesthesia for these tests. Any deterioration in the baseline values is further investigated by transbronchial biopsy, bronchoalveolar lavage, and open lung biopsy.

**KEY POINTS: PRIMARY GRAFT FAILURE, PHYSIOLOGICAL CHANGES, AND SURVEILLANCE**

- PGD occurs within 72 hours of transplant, and presents with varying degrees of hypoxemia and pulmonary edema.
- Addition of PEEP, diuresis, inotropic support, and veno-venous ECMO are support modalities.
- Transplanted lungs continue to grow in infants and children, in both larger airways and lung parenchyma, including an increase in the number of alveoli.
- Serial pulmonary function tests and bronchoalveolar lavage with biopsies are performed as routine surveillance monitoring.

**Surgical complications**

**Airway complications**
The blood supply to the donor bronchus and bronchial anastomosis is compromised during lung transplant surgery. Inadequate blood supply can result in poor healing at the anastomotic site and other airway complications such as airway stenosis, development of granulation tissue, tracheomalacia, and rarely airway dehiscence. Surgical techniques such as the use of peri-bronchial tissue around the anastomotic site and the use of a smaller segment of donor bronchus can minimize the incidence of these complications. In a single-center study involving 239 transplant surgeries, Choong et al. reported that 13% of children needed surgical interventions for their airway complications [113]. Preoperative bacterial and fungal infections, longer ischemic times, and prolonged mechanical ventilation were identified as significant risk factors. In this study, younger age of the patient was not identified as an independent risk factor for developing airway stenosis. However, infants may have a higher incidence of developing tracheomalacia and dynamic obstruction of major airways. Most patients with tracheo-bronchomalacia show significant improvement without any surgical interventions, but may need prolonged mechanical ventilation [114]. Usually airway complications are diagnosed within the first 3 months of surgery. Airway stenosis is usually treated successfully with repeated mechanical balloon dilatation through a rigid bronchoscope. Children with recurrent airway stenosis after repeated balloon dilations may require mechanical stents to maintain airway patency.

**Vascular complications**
Vascular complications are rare, mostly presenting in the form of obstruction to the blood flow in pulmonary veins. Significant pulmonary venous obstruction presents immediately after weaning off bypass or in the immediate postoperative period. Clinical signs include persistent hypoxemia and pink frothy secretions in the airway, along with increased pulmonary arterial pressures. Perfusion scans may be performed in transplant patients after their lung transplant surgery, to rule out any undiagnosed discrepancy of pulmonary flow to either lung. If pulmonary venous obstruction is suspected, a definitive diagnosis can be made during cardiac catheterization. Any significant obstruction to pulmonary blood flow requires an urgent treatment with either surgical correction or placement of a stent in the cardiac catheterization laboratory.

**Nerve injuries**
Injuries to nerves that lie adjacent to the bronchopulmonary tissue are frequently injured during the transplant surgery. Huddleston reported a 22% incidence of phrenic nerve injury in children [114]. The resulting diaphragmatic paralysis is usually a transient phenomenon but can prolong the need for mechanical ventilation and intensive care stay. Injury to the vagus nerve frequently leads to gastro-esophageal reflux and gastric paresis. Severe gastric paresis and resulting recurrent silent aspiration have been implicated in deteriorating graft function and resulting bronchiolitis obliterans. The incidence of severe gastro-esophageal reflux is as high as 50%. Younger patients are especially susceptible to this injury and many neonatal and infant lung recipients require fundoplication after their transplant surgery. Patients with deteriorating...
Arrhythmias

A large atrial suture line is a potential source for generating abnormal depolarization and repolarization. Clinically significant atrial flutter requiring medical treatment is seen in about 11% of pediatric patients. Supraventricular tachycardia and atrial fibrillation are also seen. Most arrhythmias are amenable to medical treatment alone.

**KEY POINTS: SURGICAL COMPLICATIONS**

- Airway stenosis, tracheomalacia, granulation tissue, or dehiscence is seen in approximately 13% of pediatric lung transplant recipients.
- Pulmonary vein obstruction is a serious complication heralded by hypoxemia and pink frothy secretions.
- Phrenic nerve, recurrent laryngeal nerve, and vagus nerve injuries are relatively frequent complications after lung transplantation in children.

Medical complications

**Graft rejection, immunosuppressive therapy, and drug interactions**

Transplanted lungs have a large endothelial surface and many immunologically active cells, making lungs more susceptible to rejection when compared with the other solid organs. Recurrent graft rejections are more common after lung transplantation compared with other solid organ transplant surgeries. Infants and younger children appear to be somewhat protected and suffer from fewer episodes of acute rejection [92,93]. This discrepancy can be explained by their relatively immature immune system. The clinical picture of rejection is a non-specific deterioration in the functional status or pulmonary function parameters. These clinical findings are further investigated by transbronchial or open lung biopsy. Once the diagnosis of acute rejection is made, these episodes are treated aggressively with a course of intravenous drugs such as high-dose steroids, antithymocyte globulin, and tacrolimus.

For chronic immunosuppression, most children are given a triple drug therapy including calcineurin inhibitor (cyclosporine or tacrolimus), cell cycle inhibitors such as azathioprine or MMF, and prednisone. Chronic use of these drugs causes complications such as compromised renal function, hypertension, hypercholesterolemia, hirsutism, and osteoporosis. About 30% of children have clinically significant renal dysfunction, but many others demonstrate subclinical renal dysfunction with borderline serum creatinine levels. As a large number of these children are at risk of developing renal failure, nephrotoxic drugs such as non-steroidal anti-inflammatory agents should be avoided even if renal function is normal. CF patients, because of the unreliable gastric absorption and hepatic clearance, are at risk for developing acute toxicity from oral medications like cyclosporine. In fact, the high incidence of central nervous complications like seizures, headache, and stroke has been attributed to acute increases in plasma levels of cyclosporine. Hepatic enzymes such as cytochrome P450 metabolize commonly used immunosuppressant drugs. Drugs that are commonly used during surgery (e.g., metoclopramide, barbiturates, etc.) induce cytochrome P450, resulting in dangerously low levels of cyclosporine.

**Opportunistic infections**

A high degree of immunosuppression is needed after lung transplantation and also adds to the risk of bacterial and viral infections. Bacterial infections are most common,
but fungal and viral infections tend to have higher mortality. Cytomegalovirus, adenovirus, Ebstein–Barr virus, and influenza are the common infections. Physiological consequences of denervation, e.g., poor cough effort, poor mucociliary clearance of secretions, and anastomotic stenosis, also contribute to these patients’ tendency to develop frequent infections. Cytomegalovirus infection is associated with an increased incidence of acute and chronic rejection. Preoperative infection with aspergillosis is often seen in CF patients, requiring prolonged treatment with antifungal drugs such as voriconazole.

**Post-transplant lymphoproliferative disorder**

Post-transplant lymphoproliferative disorder mostly results from B-cell proliferation and is commonly seen in patients with T-cell depletion. The incidence of PTLD is 8.2% at 5 years and is mostly related to Epstein–Barr virus infection. The hyperplasia of the lymphatic tissue is seen in intra-thoracic tissue as lung nodules and mediastinal lymphadenopathy. It can also present in extra-thoracic tissues, such as tonsillar hypertrophy, cerebral and visceral masses. Most children will respond to a reduction in immunosuppression but chemotherapy may be needed in a few unresponsive patients.

**Obliterative bronchiolitis and bronchiolitis obliterans syndrome**

Bronchiolitis obliterans syndrome (BOS) remains the Achilles heel of lung transplant surgery and is the most common form of chronic lung allograft dysfunction (CLAD). It is the leading cause of death after the first year of transplant surgery and continues to be a major challenge for the long term success after pediatric lung transplantation. Roughly half the surviving children develop obliterative bronchitis (OB) by 5 years after their lung transplant surgery [115]. In addition to increasing mortality, BOS causes significant morbidity and impairs quality of life after lung transplant. A number of factors, such as duration of the ischemic time, number of rejections, and age of the recipient at the time of surgery, appear to influence the incidence of the disease. In a retrospective analysis, children with total ischemic time of less than 2 hours had significantly lower incidence of OB, when compared with a similar group of patients with longer ischemic time (20% vs. 52%) [116]. In general, patients transplanted with mature living donor lobes tend to have shorter ischemic times. This may also explain a lower incidence of OB in these patients. The incidence of OB is also lower in smaller children (age < 3 years at the time of transplant). This is presumably related to a lower annual incidence of acute rejection compared with the older children (0.2 episodes compared with 1.95). OB is a histological diagnosis reflecting inflammatory and fibroproliferative changes in the bronchioles of children with chronic graft dysfunction. As the histological diagnosis is difficult to make, BOS, a corresponding clinical syndrome, is used to describe a non-specific, significant, progressive, and non-reversible decline in airflow. For older children, a 20% decrease in the baseline FEV₁ is a reliable indicator for BOS. The exact mechanism of OB is still not known, but recent research suggests that a number of immune-mediated and immune-independent mechanisms are responsible. Alloimmune-mediated mechanisms cause injury by acute rejection, cellular lymphocytic bronchiolitis, activation of humoral immune system, and autoimmune dysfunction. A number of immunity-independent mechanisms such as infections, aspiration, ischemia, and primary graft failure also appear to contribute to this irreversible and mostly progressive deterioration of the pulmonary architecture. Injury caused by these mechanisms induces a significant fibrotic reaction, remodeling, and abnormal angiogenesis. A subgroup of CLAD that does not demonstrate restrictive function may stabilize with aggressive treatment with azithromycin and photophoresis [115]. Enhanced immunosuppression is the cornerstone of currently used therapies, though none of the methods have been able to show a consistent benefit to all patients. Anti-reflux surgery may also prevent or even reverse the decline in pulmonary function in some patients. Statins like pravastatin, because of their ability to induce apoptosis in fibroblasts, may hold some promise in treating BOS. Retransplantation is considered in relatively few patients; however, the risk of post-surgical death within 1 year is high.

**Living donor lobar lung transplant**

Living donor lobar lung transplant (LDLLT) is considered as an acceptable alternative to cadaveric lung transplant in few patients who are not expected to survive to receive cadaveric lungs or patients who are listed for retransplantation. In this procedure, lower lobes from two healthy living related donors are transplanted into a single recipient. In order to provide adequate lung volume to the recipient and provide at least 50% of the predicted lung volume, this procedure has been primarily used for children or small adults. LDLLT presents a serious ethical dilemma of subjecting two healthy adults to a procedure with the potential of serious complications (10–20%) and an inevitable 15–20% reduction in pulmonary function.
Pairwise comparisons were not significant at $P < 0.05$

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<tr>
<td>6–10 years</td>
<td>29</td>
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<tr>
<td>11–17 years</td>
<td>12</td>
</tr>
</tbody>
</table>

**Figure 27.10** Kaplan–Meier survival by recipient age group (pediatric lung transplants: January 1990–June 2011). (Source: Benden [91]. Reproduced with permission of Elsevier.)

[117]. There has been a recent decline in the number of centers performing LDLLTs. Only three centers have reported significant experience with living related transplant surgeries. As these surgeries are done in a more controlled environment, ischemic times are shorter. As a result, the incidence of PGD and bronchiolitis is low [118]. Recently, Date reported a very encouraging 87.6% 5-year survival rate from LDLLT in 43 adult and pediatric patients [119]. However, ISHLT data suggest no advantage in 5-year survival in pediatric patients receiving living related donor lungs.

**Mortality and long-term survival**

Overall, lung transplant recipients do not live as long as the recipients of other solid organ transplants. The results of pediatric lung transplantation, although comparable to adults, remains worse than other solid organs transplant surgeries (see Figure 27.10). Mortality is greatest in the first year after surgery and approximately 15% of transplanted children succumb to infection and graft failure. Long-term survival after pediatric lung transplantation remains similar to that reported in adults, with a median survival of 4.3 years. It appears that children who were transplanted after 2002 have much better survival rates (81% and 58% at 1 and 4 years, respectively) [1]. Single-center data from St. Louis Children hospital suggest that infants have higher early mortality (25% vs. 4.9%) but significantly better long-term outcome than children above 11 years of age (survival half-life of 6.5 vs. 4.5 years). However, recent ISHLT registry data suggest that survival conditional on survival to 1 year is the same as in older children. PGD is the leading cause of early mortality and accounts for 62% of early deaths. BO, infection, and PTLD are usually responsible for the poor long-term outcome. Pre-transplant diagnosis of pulmonary hypertension and children undergoing repeat transplant appear to have relatively poorer outcome.

So far no prospective studies analyzing the benefit to pediatric patients have been conducted. Recently, Liou et al. performed a Cox proportional hazards analysis in children with CF, using transplant surgery as a time-dependent covariate [120]. The authors observed that, based on the recent data from the OPTN database, children with a 5-year life expectancy less than 50% at the time of transplant showed no difference from the non-transplanted group with a similar severity of disease. Among 127 children with a 5-year predicted survival greater than 50%, the transplanted group showed a substantial decrease in post-transplant survival when compared with the control non-transplant group. It was concluded that benefit from lung transplantation for CF patients could no longer be assumed. However, the study did not include impact of the recent changes in the lung allocation system and the authors were unable to comment on the improvements in the quality of life in CF children after transplant surgery. Another limitation of the study was that it included covariates obtained 2–3 years prior to the surgery and did not account for the medical condition of the patient at the time of transplant. Impact of this highly invasive surgery on the quality of life years survived has not been well studied in lung transplant pediatric patients. Future studies are needed to clarify the potential benefit of lung transplant surgery in children with CF and other disease leading to end-stage pulmonary failure.

**KEY POINTS: MORTALITY AND LONG-TERM SURVIVAL**

- Overall, pediatric lung transplant survival is worse than other solid organ transplants.
- Median survival since 1990 is 4–6 years, with patients < 10 years having slightly longer survival.
- Since 2002, survival has improved slightly in pediatric lung transplant recipients.
Selected references
A full reference list for this chapter is available at:
http://www.wiley.com/go/andropoulos/congenitalheart


Incidence, anatomy, and natural history

Definition
Pulmonary hypertension (PH) has many different etiologies which all share the final common path of elevated pulmonary arterial pressure (PAP). After birth, PAP falls reaching adult levels within a few months. In normal, healthy individuals mean pulmonary artery pressure (mPAP) at rest is around 15 mmHg, and is independent of age, ethnicity and gender. During exercise, mPAP increases and is dependent on the level of exertion and age. During mild exercise, mPAP is 20 ± 5 mmHg in subjects under age 50 years compared with 30 ± 5 mmHg in subjects older than age 50 years, which makes it difficult to define normal mPAP during exercise, and hence the definition of PH uses mPAP at rest [1]. In adults and children, PH is defined as mPAP > 25 mmHg at rest. This definition does not carry any implication of the presence or absence of pulmonary hypertensive vascular disease. Pulmonary vascular resistance (PVR) is important in the diagnosis and management of pulmonary hypertensive vascular disease in patients with congenital heart disease (CHD). PH complicates the course of many children and adults with CHD. The increase in PAP associated with CHD is secondary to either increased “pre-capillary” pulmonary blood flow (left-to-right shunt lesion) or increased post-capillary pressures (left heart disease). Based on the hemodynamic definition of PH (mPAP > 25 mmHg), almost all patients with a large unrestricted left-to-right shunt will have PH. What is important in this setting is the degree of pulmonary hypertensive vascular disease resulting in an increase in PVR. A patient with a high pulmonary blood flow and low PVR will have PH but can be safely treated with closure of the shunt. On the contrary, a patient with low pulmonary blood flow, shunt reversal (right to left), cyanosis and high PVR, so-called Eisenmenger syndrome, will be harmed with shunt closure due to worsening right heart failure as there is no longer a “pop-off” for blood flow [2]. Eisenmenger syndrome is an end-stage, and usually irreversible, cause of PH with a high pulmonary vascular resistance index (PVRI) > 10 Wood units/m² with reversed or bi-directional shunting of blood at an aortopulmonary, ventricular, or atrial level. However, between these two extremes of PH and associated CHD is a challenging gray zone that requires careful diagnostic evaluation to guide future management.

Classification
Pulmonary hypertension can be clinically classified according to an internationally recognized classification. The original classification of PH was conceived at the 1998 second World Symposium on Pulmonary Hypertension held in Evian, France. The classification underwent revisions at subsequent symposia and most recently at the
5th World Symposium held in Nice, France in 2013 [3]. The current clinical classification of PH has five categories based on shared pathological mechanisms (Box 28.1). Until this most recent symposium in Nice, the classification system for children had been problematic, as it did not reflect the complex heterogeneity of factors that contribute to pediatric PH. As a result, the Pulmonary Vascular Research Institute Pediatric Taskforce proposed a new classification of pediatric PH at its meeting in Panama in 2011 [4]. The classification is 10 categories based on clinical pediatric practice and reflects the heterogeneous nature of pediatric PH (Table 28.1). The Panama classification includes an additional definition of PH for children with univentricular circulations: following a cavopulmonary anastomosis PH is defined as a PVRI > 3 Wood units x m² or a transpulmonary gradient (mPAP – LAP) > 6 mmHg even if the mPAP is < 25 mmHg (Box 28.2) [4,5]. In this setting of non-pulsatile blood flow to the pulmonary arteries, even though mPAP may not be greater than 25 mmHg, significant pulmonary hypertensive vascular disease can lead to a poor outcome. With the agreement of the Pediatric Taskforce, some of these items were included in the most recent 2013 Nice Pulmonary Hypertension Classification, in order to have a more comprehensive classification, inclusive of both adults and children [6].

### Box 28.1: Classification of pulmonary hypertension

1. Pulmonary arterial hypertension (PAH)
   1.1. Idiopathic PAH
   1.2. Heritable PAH
      1.2.1. BMPR2
      1.2.2. ALK-1, ENG, SMAD9, CAV1, KCNK3
      1.2.3. Unknown
   1.3. Drug and toxin induced
   1.4. Associated with:
      1.4.1. Connective tissue disease
      1.4.2. HIV infection
      1.4.3. Portal hypertension
      1.4.4. Congenital heart disease
      1.4.5. Schistosomiasis

2. Pulmonary hypertension with unclear multifactorial mechanisms

3. Pulmonary hypertension due to lung diseases and/or hypoxia
   3.1. Chronic obstructive pulmonary disease
   3.2. Interstitial lung disease
   3.3. Other pulmonary diseases with mixed restrictive and obstructive pattern
   3.4. Sleep-disordered breathing
   3.5. Alveolar hypventilation disorders
   3.6. Chronic exposure to high altitude
   3.7. Developmental lung diseases

4. Chronic thromboembolic pulmonary hypertension (CTEPH)

5. Pulmonary hypertension with unclear multifactorial mechanisms
   5.1. Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
   5.2. Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
   5.3. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
   5.4. Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

ALK, activin-like receptor kinase; BMPR, bone morphogenetic protein receptor; CAV, caveolin; ENG, endoglin; SMAD, fusion of gene names SMA (in C. elegans) and MAD (in Drosophila); KCNK, potassium channel sub-family K; HIV, human immunodeficiency virus.

Source: Simonneau et al. [3]. Adapted with permission of Elsevier.

### Table 28.1 The Panama Classification: 10 categories of pediatric pulmonary hypertensive vascular disease

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Prenatal or developmental pulmonary hypertensive vascular disease</td>
</tr>
<tr>
<td>2</td>
<td>Perinatal pulmonary vascular maladaption</td>
</tr>
<tr>
<td>3</td>
<td>Pediatric cardiovascular disease</td>
</tr>
<tr>
<td>4</td>
<td>Bronchopulmonary dysplasia</td>
</tr>
<tr>
<td>5</td>
<td>Isolated pediatric pulmonary hypertensive vascular disease</td>
</tr>
<tr>
<td>6</td>
<td>Multifactorial pulmonary hypertensive vascular disease in congenital malformation syndromes</td>
</tr>
<tr>
<td>7</td>
<td>Pediatric lung disease</td>
</tr>
<tr>
<td>8</td>
<td>Pediatric thromboembolic disease</td>
</tr>
<tr>
<td>9</td>
<td>Pediatric hypobiliary hypoxic exposure</td>
</tr>
<tr>
<td>10</td>
<td>Pediatric pulmonary vascular disease associated with other system disorders</td>
</tr>
</tbody>
</table>

Source: Cero et al. [4]. Adapted with permission of Medknow.

### Box 28.2: The modern definition of pulmonary arterial hypertension in children with biventricular and palliated univentricular circulations

**Biventricular circulation**
- mPAP > 25 mmHg and PVRI > 3 Wood units x m²
- Positive vasodilator response defined as a fall in mPAP and PVRI by 20% with no change in CO

**Univentricular circulation**
- Following palliation with a cavopulmonary anastomosis
- PVRI > 3 Wood units x m² or TPG > 6 mmHg even if mPAP < 25 mmHg

mPAP, mean pulmonary artery pressure; PVRI, pulmonary vascular resistance index; CO, cardiac output; TPG, transpulmonary gradient

Children with CHD and PH are in group 1, pulmonary arterial hypertension (PAH), of the 2013 Nice Pulmonary Hypertension Classification. This subgroup (1.4.4) is further classified into four types. Type 1 includes patients with Eisenmenger syndrome with right-to-left shunting
and systemic desaturation. Type 2 includes patients with CHD and significant pulmonary hypertensive vascular disease with normal resting saturation. The shunts may be either operable or inoperable but are characterized by increased PVR. Type 3 includes PAH with coincidental CHD, which includes small atrial and ventricular septal defects (ASD, VSD) that do not cause severe PAH. Type 4 is postoperative PAH and includes patients with any type of repaired CHD who develop or have persisting PAH.

The 2013 Nice Pulmonary Hypertension Classification of PH group 2 includes congenital and acquired left heart inflow and outflow tract obstruction, such as pulmonary vein stenosis, cor triatriatum, mitral stenosis, and cardiomyopathies. This group causes the 'post-capillary' increase in PAP. In group 3, developmental lung diseases are emphasized due to the important role of abnormal lung vascular growth in the pathogenesis of PH. Examples include congenital diaphragmatic hernia, bronchopulmonary dysplasia, alveolar capillary dysplasia, and surfactant protein abnormalities. Group 4, chronic thromboembolic PH, and group 5, PH with unclear multifactorial mechanisms, are very rare causes of pediatric PH.

The characterization of PH according to these classifications is an essential part of the diagnostic work-up of PH. The treatment strategy and prognosis of pediatric PH largely depend on its subclass and associated conditions. It is therefore important to correctly characterize the type of PH using standardized diagnostic work-up. However, in pediatric PH, there is often more than one associated condition identified, which leaves it to the clinician to determine the contribution of each condition to the PH and to decide on which condition therapy should be focused.

**Epidemiology**

The major etiologies of pediatric PH cases are idiopathic PAH (IPAH), heritable PAH (HPAH), and PAH associated with CHD (PAH-CHD). Specific gene mutations have been have been identified in association with HPAH: bone morphogenetic protein receptor type-2 (BMPR-2), activin-like kinase-1 (ALK-1), and endoglin mutations. BMPR-2 is the most common gene mutation associated with pediatric PAH and can be identified in 10–20% of pediatric patients with IPAH/HPAH [7–9]. Two large registries have provided further insights into the etiology of pediatric PH. The Tracking Outcomes and Practice in Pediatric Pulmonary Hypertension (TOPP) registry reported 362 patients with confirmed PH [10]. Of these patients, 317 (88%) had PAH, of which 57% were characterized as IPAH or HPAH, and 36% as PAH-CHD. Only three patients had chronic thromboembolic PH. Chromosomal anomalies, mainly trisomy 21, or syndromes were reported in 47 (13%) of the patients. Another large registry for pediatric PH is from the Netherlands. This registry reports 2,845 of 3,263 (87%) pediatric patients with PAH in group 1 of the 2013 Nice Pulmonary Hypertension Classification, including transient PAH (82%) or progressive PAH (5%) [8]. The most common cause of transient PAH was persistent PH of the newborn (PPHN) (58%), and the most common cause of progressive PAH was PAH-CHD (72%). Trisomy 21 was the most frequent chromosomal abnormality (12%), a rate similar to that observed in the TOPP registry.

Pulmonary hypertension is a rare disease. The incidence and prevalence of PH in the pediatric population are not well known. In the Netherlands’ registry, the annual incidences of IPAH and PAH-CHD were 0.7 and 2.2 cases per million, respectively. The prevalence of PAH-CHD was 15.6 cases per million [8]. The national registry from the United Kingdom reports similar numbers with an annual incidence of IPAH of 0.48 cases per million children and a prevalence of 2.1 cases per million [11]. In a multicenter study in France, the estimated prevalence of PAH was 3.7 cases per million children, with IPAH (60%) and PAH-CHD (24%) being the main etiologies [12].

Survival for patients with PH has improved with the introduction of management guidelines, dedicated centers, and new drug therapies. Before targeted drug therapies were available for PH, the estimated median survival of children and adults with IPAH were similar, at 4.12 and 3.12 years, respectively [13]. After the introduction of targeted pulmonary vasodilators, the survival rate for children with PAH has continued to improve. In the combined pediatric and adult U.S. Registry to Evaluate Early and Long Term PAH Disease Management (REVEAL) registry, patients with childhood-onset PAH had 1-, 3-, and 5-year survival rates of 96%, 84% and 74%, respectively [14]. There was no significant difference in 5-year survival between IPAH/HPAH (75%) and PAH-CHD (71%). Similar data have been published from studies in the Netherlands and the UK [11,15,16]. Although overall survival has improved, patients with repaired CHD and pulmonary hypertensive vascular disease have a high mortality risk.

**Pathophysiology of PH in CHD**

Pulmonary hypertension associated with CHD is part of the 2013 Nice Pulmonary Hypertension Classification, group 1, pulmonary arterial hypertension (PAH). This group distinguishes itself from the other four categories by its characteristic pattern of vascular remodeling, progressive nature, and response to specific medical therapy. Heath and Edwards published the first description of pulmonary vascular remodeling due to CHD in 1958 [17]. They divided the histological progression into grades 1–6 in increasing severity. Later Rabinovitch developed the morphometric approach, which quantifies the thickness of the pulmonary arterial muscle, the degree of abnormal distal extension of smooth muscle, and the density of small pulmonary arteries relative to the number of alveoli [18]. The morphometric structural findings are graded from A through C in increasing severity of changes. This morphometric analysis has contributed to our understanding of pulmonary vascular remodeling by establishing that abnormal extension of smooth muscle and a reduction of
small artery density are a hallmark of pulmonary hypertensive vascular disease. This approach has emphasized that early age to correct congenital heart defects helps to preserve small pulmonary arteries and predicts good pulmonary hemodynamics postoperatively. The pulmonary vascular remodeling that is characteristic of PAH involves adventitial thickening, medial hypertrophy, and intimal proliferation, including the formation of plexiform lesions [19]. This vascular remodeling leads to arterial wall thickening and occlusion of small distal pulmonary arteries. Together with other mechanisms including vasoconstriction, inflammation, and thrombosis, the vascular wall thickening and occlusion will consequently increase PAP and PVR. This increase in right ventricular afterload increases right ventricular workload, eventually resulting in right ventricular failure.

The pulmonary vascular bed plays a key role in the presentation and management of children with almost all forms of CHD. Four variables are important in the development of pulmonary hypertensive vascular disease and whether it will regress or progress after repair of a congenital cardiac shunt lesion:

- Age of the patient at repair
- Type of cardiac lesion
- PVRI at operation
- Individual genetic and environment factors and co-morbidities.

The evolution of PAH-CHD and the age at which it presents itself depend on the type of shunt lesion. In patients with a shunt at the pre-tricuspid valve level (e.g. ASD) there is an increased pulmonary volume load with a normal pressure load. Only 5–20% of these patients will develop severe PAH, and usually not until the third or fourth decade of life [20,21]. In patients with non-restrictive shunts at the post-tricuspid valve level, the increased pulmonary volume is accompanied by an increased pressure load due to pressure equalization across the shunt defect. In these patients, PAH usually develops more rapidly during the first few years of life. If left uncorrected, these systemic-to-pulmonary shunts will result in steadily increasing PVR, and when this exceeds the systemic vascular resistance (SVR), the shunt will reverse, resulting in hypoxemia and cyanosis, which are the hallmarks of Eisenmenger syndrome [2]. For this reason, most CHD shunt lesions should be repaired within the first 2 years of life. The exact level of PVRI that precludes safe closure of a defect is often debated and varies with each lesion. The 5th World Symposium on Pulmonary Hypertension in Nice in 2013 proposed criteria for shunt closure in patients with net left-to-right shunting (Table 28.2) [3]. Complex congenital heart defects, such as transposition of the great arteries, truncus arteriosus, and aortopulmonary window, present with pulmonary hypertensive vascular disease much earlier and should therefore be repaired in the first weeks of life.

Patient genetic and environmental factors may influence the timing of repair of congenital heart defects with PAH. Pediatric PAH occurs in 20–40% of children with genetic disorders, including trisomy 21, Noonan, velocardiofacial and Jacobsen syndromes [9]. Furthermore, many children with PAH have clinical signs of a syndrome, such as dysmorphic features, which cannot be explained by a known syndrome diagnosis or genetic test. The frequent occurrence of genetic abnormalities in children with PAH suggests the existence of still unknown genetic pathways involved in the disease process of PAH. The BMPR-2 mutation has been described in 6% of children with CHD [22]. Co-morbidities may also exacerbate PAH-CHD. For example, children with trisomy 21 are at higher risk for developing PH due to sleep-disordered breathing, upper airway obstruction, silent aspiration with recurrent pneumonias, and pulmonary hypoplasia [23]. The net result comprises episodes of hypoxia, which in turn may exacerbate the pulmonary vascular disease from CHD. In developing countries, there may be additional co-morbidities to consider. In Africa, in a cohort of children with CHD, 53% were anemic, 47% underweight, and 33% had marasmus compared with a control group without CHD, of whom none had marasmus and only 14% were underweight [24]. Tuberculosis is twice as common in patients with CHD, especially in those with lesions with an increased pulmonary blood flow, and if treatment is available, the major cause of morbidity is delay of cardiac surgery [25]. Unfortunately, tuberculosis may mask the signs of CHD and result in a delay in diagnosis of CHD and subsequent surgical repair. Human immunodeficiency virus (HIV) infection is endemic in sub-Saharan Africa. In Uganda, CHD affects 5% of children with HIV compared to 3% in developed countries [26]. The interaction between genetic susceptibility to PH and CHD, and other factors, such as nutrition and infection, is complex and not fully understood.

Environmental factors may also influence the timing of surgical repair of congenital heart defects. High altitude has effects on normal neonatal pulmonary vascular transition, which is related not only to altitude but also to ancestry. Ethnic groups with recent migration to high

<table>
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<tr>
<td>&gt;8</td>
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</tr>
<tr>
<td>4–8</td>
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Table 28.2 Criteria for closing cardiac shunts in PAH patients associated with congenital heart defects

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*aCriteria: the long-term impact of defect closure in the presence of pulmonary arterial hypertension (PAH) with increased pulmonary vascular resistance (PVR) is largely unknown. There is a lack of data in this controversial area and caution must be exercised.

*bCorrectable: with surgery or intravascular non-surgical procedure
PVRI, pulmonary vascular resistance index.

Source: Simonneau et al., 2013 [3]. Adapted with permission of Elsevier.
```
altitude have lower oxygen saturations and higher PAP than those with a long ancestry of high-altitude living, such as native residents of the Andes mountain range and Tibet. In addition, the incidence of CHD increases at higher altitude, the ductus arteriosus is larger and its closure delayed, with a higher pulmonary to systemic blood flow ratio for a given PVR. As a result, management decisions, particularly the timing of surgical repair, are different at high altitude [27,28].

KEY POINTS: CLASSIFICATION AND DEFINITION OF PH

- The current 2013 classification of PH incorporates factors that are common to both children and adults with the disease.
- There are different definitions for PH in children than in adults, including separate definitions for biventricular and univentricular circulations.

Assessment of PH

The clinical assessment of the child with PAH and CHD is aimed at differentiating those with reversible pulmonary vascular disease who are operable, from those with irreversible or fixed disease. In cases that are not straightforward, it is important to put together all of the clinical information without relying on one single parameter. The clinical presentation of pediatric PH is non-specific and age-dependent. The most common presenting symptom is reduced exercise capacity accompanied by fatigue and dyspnea. Young infants may present with feeding problems and failure to thrive. Other presenting symptoms include cyanosis, cough, and chest or abdominal pain. Syncope as a presenting symptom is specific to pediatric PH, is reported in 25–30% of children with PH and is most frequent in patients without a shunt defect [9–11]. There is often a long delay between onset of symptoms and diagnosis due to the low specificity of presenting symptoms and the rarity of the disease. Screening should take place for children belonging to high-risk groups based on underlying conditions of family members with PH.

The functional status of children and adults with PH, with respect to exercise capacity and symptoms, can be classified using the World Health Organization (WHO) functional class [29]. Although the WHO functional class is not designed specifically for children, it has been shown to correlate with 6-minute walk distance and hemodynamic parameters [12,14,15,30]. Although not validated, a functional class designed specifically for children has been proposed [31].

After a thorough history and physical examination of the patient, blood should be drawn for laboratory analysis, including complete blood count, metabolic panel, coagulation profile, and biomarkers of PH. Biomarkers that specifically indicate the pathologic mechanism, the severity of the disease, and the treatment response would be ideal tools for the management of PH, but they are still the subjects of research. Anemia, hypocarbia, elevated uric acid, and C-reactive protein levels are non-specific markers of disease severity. Brain natriuretic peptide and N-terminal fragment of pro-brain natriuretic peptide, which reflect the degree of atrial stretch and heart failure, are recommended for disease monitoring [32].

Non-invasive imaging for the assessment of PH includes; chest X-ray, echocardiography, CT-scan of the lungs, nuclear medicine ventilation perfusion scan, and magnetic resonance imaging (MRI). A chest X-ray provides information on the heart size and the pulmonary vasculature. Echocardiography provides information about the anatomic details of the lesion, assessment of shunt direction, and estimates of PAPs [33]. Echocardiography may support the diagnosis of PH with qualitative images of elevated right ventricular pressure, such as right ventricular hypertrophy and septal wall flattening. Quantitative information may be obtained on echocardiography if there is tricuspid regurgitation during systole (Figure 28.1). In this case, the modified Bernoulli equation may be applied to estimate PAP, with a tricuspid regurgitant velocity of greater than 2.8 m/s being highly indicative of PAH (Box 28.3) [1,34]. Measurement of the end-systolic right to left ventricular (RV/LV) diameter ratio correlates with invasive measurements of the severity of PH [35]. Echocardiography can provide information on the direction of flow through a shunt. A pure left-to-right shunt across a defect indicates that the PVR is lower than the SVR. The presence of reversed or bi-directional flow across an ASD, patent ductus arteriosus or VSD is concerning and suggests the need for cardiac catheterization and acute vasoreactivity testing. Transthoracic echocardiography is an attractive method to assess children with PH and possibly enable the cardiologists to lengthen the interval between cardiac catheterizations required to monitor ongoing therapy. There are many echocardiographic techniques in the research and validation phase. One technique is to monitor the right ventricular systolic to diastolic duration ratio, in which an

Box 28.3: Estimating PAP from systolic tricuspid regurgitant jet velocity on echocardiography

Modified Bernoulli equation

\[ sPAP = 4v^2 + RAP \]

e.g. \[ sPAP = 4(2.8^2) + 10 = 41 \text{ mmHg} \]

Converting \( sPAP \) to \( mPAP \)

\[ mPAP = (0.61 \times sPAP) + 2 \text{ mmHg} \]

e.g. \[ mPAP = (0.61 \times 41) + 2 = 27 \text{ mmHg} \]

\( sPAP \): systolic pulmonary artery pressure; \( RAP \): right atrial pressure; \( mPAP \): mean pulmonary artery pressure; \( v \): tricuspid regurgitation velocity using Doppler echocardiography.
increase has been shown to be associated with worse right ventricular function, exercise capability, and survival [36]. Another technique using echocardiography is to measure the degree of tricuspid annular plane systolic excursion (TAPSE), which has been shown to reflect right ventricular function and prognosis in PH [37,38].

Magnetic resonance imaging is increasingly being used to evaluate children with PAH and CHD. MRI can determine pulmonary blood flow, which may be especially useful if there are multiple sources of pulmonary blood flow, such as aortopulmonary collateral vessels. MRI will also measure right ventricular volumes accurately [39]. The combination of MRI and direct PAP measurement may provide more information than either test alone.

Despite advances in non-invasive imaging techniques, cardiac catheterization with vasodilator testing is necessary for diagnosis, treatment stratification and prognosis of PH in children [40]. There are three objectives during the catheterization procedure: to obtain hemodynamic data, to test vasoreactivity, and to rule out any associated disease states. Accurate hemodynamic data are essential for the diagnosis and ongoing monitoring of patients with PH. End-hole or flow-directed catheters are used to obtain hemodynamic data. Catheters with multiple side holes are used for angiography to prevent myocardial staining during injection. During catheterization, baseline measures include right atrial pressure, PAP, systemic arterial pressure, mixed venous and systemic arterial saturation, cardiac output, and pulmonary artery occlusion pressure. From these measures, important calculations can be made for pulmonary to systemic flow ratio (Qp:Qs) (Box 28.4) and PVR (Box 28.5) [41,42]. It is essential that the anesthesiologist maintains the patient’s hemodynamic and ventilatory stability during these periods of measurement and that the conditions under which they are made are clearly communicated. Most cardiac catheterization laboratories will obtain baseline measurements in room air, followed by 70–100% oxygen, and then introduce an acute vasodilator such as inhaled nitric oxide (iNO) 20–40 parts per million (ppm). In a recent review of cardiac catheterization laboratory protocols and hemodynamic data in pediatric patients with PH, general anesthesia was
found to decrease systemic arterial pressure, but there was no difference between general anesthesia and procedural sedation on mPAP or PVRI. It also demonstrated that pediatric patients with PH demonstrate a higher incidence of PH associated with CHD and neonatal specific disorders compared with adults. The review also points out that pediatric PH patients had baseline mPAP compared with adults. The review also points out that pediatric patients with PH demonstrate a higher incidence of PH associated with CHD and neonatal specific disorders compared with adults.

The factors leading to an increase in mPAP may all occur acutely by the administration of fast-acting, short-duration vasodilators reflecting the extent to which vascular smooth muscle constriction is contributing to the hypertensive state. The response to vasodilators has important therapeutic implications in PH and almost all patients will undergo a vasodilator trial during their initial cardiac catheterization. Three separate situations may be evaluated with the acute vasodilator trial: potential treatment with calcium channel blockers (CCBs), assessment of operability in children with CHD, and determining prognosis. Intravenous epoprostenol, intravenous adenosine, and iNO are commonly used for acute vasodilator testing. The definition of a positive vasodilator response in adults is a reduction in mPAP by at least 10 mmHg, and this number must be lower than 40 mmHg. The pediatric definition of a positive response to vasodilators is a fall in mPAP and PVRI by 20% with no significant change or increase in cardiac index. Such responders are likely to have a beneficial hemodynamic and clinical response to treatment with calcium-channel-blocking drugs. It is estimated that 70–90% of children with severe PH are non-responders to acute vasodilator testing and therefore require therapy other than calcium channel antagonists [5,44]. In the cardiac catheterization laboratory, balloon occlusion of a shunt is the best means of demonstrating the short-term effect of shunt closure on PAP. It must be emphasized that cardiac catheterization of children with PH should be performed in experienced centers able to manage potential complications such as PH crisis requiring extracorporeal membrane oxygenation (ECMO) support [45,46].

**KEY POINTS: ASSESSMENT OF PH**

- A comprehensive evaluation of patients with newly diagnosed PH is essential to determine management and prognosis.

**Medical management of pulmonary arterial hypertension**

The factors leading to an increase in mPAP may all eventually result in increased PVR and pulmonary hypertensive vascular disease. As the pulmonary vasculature remodels in PAH, there are changes that may be reactive or fixed. Reactive changes will result in vasodilation of the pulmonary vasculature to an exogenously administered pulmonary vasodilator such as iNO. Fixed changes are unreactive to such pulmonary vasodilators. As the disease processes leading to PAH progress, the cross-sectional area of the pulmonary vasculature decreases according to Poiseuille’s law, leading to increased PVR. Poiseuille’s law states that the resistance of a vessel is proportional to the fourth power of the radius. In other words, as the pulmonary arterioles develop thickening of their walls and a smaller intra-luminal radius, the resistance will increase exponentially. A pulmonary hypertensive crisis is an acute-on-chronic increase in PVR during the periposition period due to an acute increase in vascular tone of the reactive portion of the pulmonary vasculature. Early recognition and appropriate management of a pulmonary hypertensive crisis can be life-saving.

The current treatment strategies for PAH are aimed at three pathological processes. Vasodilators treat reactive vasoconstriction, anti-proliferative drugs attenuate vascular remodeling, and anticoagulation may be used to treat and prevent thrombosis from forming in narrowed vessels. On the basis of the understanding of abnormalities of the vascular endothelium, three classes of pulmonary vascular vasodilating drugs have been studied for the treatment of PAH: prostacyclin analogs, endothelin receptor antagonists (ERAs), and phosphodiesterase-5 (PDE-5) inhibitors (Figure 28.2) [47–49]. The beneficial effects of these drugs, including increased exercise capacity, improved quality of life and increased survival, have been demonstrated mainly in adults. Due to the complex etiology and relative lack of data in children with PAH, selection of appropriate therapies remains difficult. A treatment algorithm based on expert opinion was proposed at the World Symposium on Pulmonary Hypertension in 2013 (Figure 28.3) [6].

The ultimate management goals of PAH in children are to increase survival and allow the normal activities of childhood without the need to self-limit. Supportive therapies may include the use of oxygen, anticoagulants, and digoxin. Diuretics may be used, but care should be taken not to decrease intravascular volume due to the preload dependence of the right ventricle. Although no controlled data exist, vaccination against influenza and pneumococcal disease is recommended in children and adults with PAH, and respiratory syncytial virus prophylaxis should be considered in infants with PAH [50,51].

**Calcium channel blockers**

Acute responders to vasodilator testing are treated with CCBs such as amlodipine, nifedipine, and diltiazem. CCBs inhibit the calcium influx through the slow channel into the cardiac and smooth muscle cells, causing relaxation of the pulmonary vascular smooth muscle. Adults with IPAH, who were acute responders to vasodilator testing and treated with CCBs, showed improved 5-year survival (94%) compared with those not treated with CCBs (55%) [52]. However, because CCBs may have negative inotropic
effects in young children, they should be avoided until the child is older than 1 year of age [53,54].

**Prostanoids**

Patients with PAH have reduced expression of prostacyclin synthetase in the pulmonary arteries [55]. The prostanoids, which are prostacyclin analogs, act via cyclic adenosine monophosphate (cAMP) in the smooth muscle cell to produce vasodilation. They may also have some anti-proliferative effects.

**Epoprostenol (Flolan®)**

This prostacyclin analog has a very short half-life (3–6 minutes) and needs to be administered continuously, usually through a permanent central venous catheter. Side-effects include facial flushing, headache, jaw pain, and abdominal pain.

**Treprostinil (Remodulin®, Tyvaso®)**

This prostacyclin analog has a longer half-life (4–5 hours) but was designed to be administered by subcutaneous injection. Pain at the injection site severely limits the use of this drug in children; subcutaneous infusion has been utilized in some patients. For those able to tolerate frequent subcutaneous injections, the side-effects are similar to epoprostenol. Other administration routes are under investigation, and the inhaled route is approved for adult patients and has been shown to be effective [56–58].

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*Figure 28.2* Therapeutic drug targets in pulmonary arterial hypertension. At the top of the figure, a transverse section of a small pulmonary artery from a patient with severe pulmonary arterial hypertension shows intimal proliferation and medial hypertrophy. Dysfunctional pulmonary artery endothelial cells (blue) have decreased production of prostacyclin and endogenous nitric oxide, with an increased production of endothelin-1, a condition promoting vasoconstriction and proliferation of smooth muscle cells in the pulmonary arteries (red). (Source: Humbert et al. [49]. Reproduced with permission of the Massachusetts Medical Society.)
Iloprost (Ventavis®)
This prostacyclin analog is delivered by the inhaled route, and because of its short half-life (20–30 minutes) it needs to be administered six to nine times per day. This frequency of administration, in addition to the side-effect of increased lower airway reactivity, has limited its use in the chronic treatment of children with PAH [59].

Endothelin receptor antagonists
Endothelin is a potent endogenous vasoconstrictor that acts via the endothelin type 1 receptor (ET). This ET receptor has two subtypes, ET_A and ET_B, which are present in pulmonary vascular smooth muscle cells, producing vasoconstriction when activated. ET_B receptors are also present in the pulmonary vascular endothelium and, when activated, produce vasodilation. Despite the differences in receptor subtype activity depending on location, both non-selective ET_A/ET_B receptor antagonists (Bosentan [Tracleer®]) and selective ET_A receptor antagonists (Ambrisentan [Letairis®]) are similarly effective in patients with PAH. Both ERAs may be administered via the oral route and require close monitoring of liver function tests.

Phosphodiesterase-5 inhibitors
Nitric oxide acts via a cyclic guanosine monophosphate (cGMP) pathway in the pulmonary artery smooth muscle cell to produce vasodilation. This pathway may be stimulated directly with iNO, or the breakdown of cGMP may be inhibited by PDE-5 inhibitors, resulting in increased cGMP and pulmonary vascular vasodilation. These inhibitors also have antiproliferative effects.

Sildenafil (Revatio®)
Sildenafil is an oral PDE-5 inhibitor usually administered three times daily. Pediatric PAH treatment with sildenafil has changed significantly since the STARTS-1 and -2 trials (Sildenafil in Treatment-Naïve Children with PAH) [60]. These trials were worldwide, randomized, double-blind, placebo-controlled studies of oral sildenafil monotherapy in low, medium and high doses. The studies found that functional capacity only improved with high-dose sildenafil, PVR improved with medium- and high-dose sildenafil, but mPAP was lower only with medium-dose sildenafil. However, hazard ratios for mortality were 3.95 for high vs. low dose and 1.92 for medium vs. low dose. Review of these data by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) resulted in different recommendations. Sildenafil was approved for use by the EMA in 2011 with a warning on avoiding higher doses. In 2012, the FDA issued a warning against the use of all doses of sildenafil for children with PAH [61,62].

Tadalafil (Adcirca®)
Tadalafil is an oral PDE-5 inhibitor that has the advantage of once-daily administration. Its side-effect profile is similar to sildenafil, including headache, flushing, nausea, myalgia, and nasal congestion [63].
Atrial septostomy and lung transplantation

Atrial septostomy performed in the cardiac catheterization laboratory should be considered in the child with worsening PH despite optimal medical therapy. The resulting improvement in cardiac output with decompression of the right heart is at the expense of hypoxemia. Features of a high-risk patient for this procedure include high right atrial pressure and low cardiac output, both of which increase mortality (5–15%) [64]. Atrial septostomy may be considered as an initial procedure or as a bridge to lung transplantation. An alternative procedure that has been described is the surgical creation of a palliative Potts’ shunt (descending aorta to left pulmonary artery) [65]. The optimal timing of these procedures is unclear. End-stage options for worsening PH unresponsive to therapy are lung or heart–lung transplantation. The median survival after lung transplantation in children is 4.9 years [66]. See Chapter 27 for a detailed discussed of cardiopulmonary transplantation.

KEY POINTS: MEDICAL MANAGEMENT OF PH

- Three classes of pulmonary vascular vasodilating drugs are available for the treatment of PH: prostacyclin analogs, ET receptor antagonists, and PDE-5 inhibitors.

Perioperative risk considerations

Patients with PH have a greater risk of experiencing adverse events associated with anesthesia and surgery. It has been well established in studies of adult patients that PH is a significant risk factor for perioperative morbidity and mortality [67–69]. Similarly, studies of children with PH have demonstrated a high incidence of perioperative cardiac arrest and death. Data from the Pediatric Perioperative Cardiac Arrest (POCA) registry suggest that a benchmark estimate of the incidence of perioperative cardiac arrest in all pediatric patients is 0.014% [70]. In comparison, children with PH experienced an incidence of perioperative cardiac arrest of 1.6% associated with all types of procedures and 10% associated with major surgical procedures, including cardiac surgery [71]. In a recent report of anesthesia-related mortality in children, PH was found to be present in half of the deaths [72]. Preoperative PAH has been shown to be a significant contributor to perioperative death associated with pediatric open cardiac surgery [73].

The presence of PH also adds significantly to perioperative risk in children undergoing cardiac catheterization (Table 28.3). The incidence of cardiac arrest among all children undergoing cardiac catheterization was reported to be 0.45% [74] and 0.96% [75]. This incidence increased significantly when only children with PH undergoing cardiac catheterization were considered, with reports of 0.8% [71], 1.2% [46], 2.9% [76], and 5.7% [77]. These serious complications are directly associated with the severity of PH, with supra-systemic PH patients experiencing a disproportionally greater incidence of major complications than those with systemic or subsystemic PH (Figure 28.4) [46,76].

Pulmonary hypertensive crisis

Cardiac arrest in children with PH is often immediately preceded by an acute pulmonary hypertensive crisis, in which an acute increase in PVR leads to right ventricular failure and a decrease in cardiac output. The right ventricle dilates and encroaches on the left ventricle, thus decreasing left ventricular stroke volume, cardiac output, and mean systemic arterial pressure (MAP). Systemic hypotension then causes a decrease in coronary perfusion pressure, which exacerbates right ventricular failure and causes biventricular ischemia. Monitors will demonstrate an increase in PAP accompanied by decreases in SpO2 and systemic blood pressure, due to inadequate pulmonary blood flow and left heart filling. The self-perpetuating cycle of biventricular failure associated with a pulmonary hypertensive crisis is illustrated in Figure 28.5.

Table 28.3 Estimated incidence of perioperative cardiac arrest and death in children with pulmonary hypertension (PH) compared with all children

<table>
<thead>
<tr>
<th>Population and reference</th>
<th>Procedures (n)</th>
<th>Cardiac arrest (%)</th>
<th>Death (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All children [70]</td>
<td>All types (1,089,200)</td>
<td>0.014</td>
<td>0.004</td>
</tr>
<tr>
<td>Children with heart disease [74]</td>
<td>Cardiac catheterization (4,454)</td>
<td>0.49</td>
<td>0.08</td>
</tr>
<tr>
<td>Children with heart disease [75]</td>
<td>Cardiac catheterization (7,289)</td>
<td>0.96</td>
<td>0.05</td>
</tr>
<tr>
<td>Children with PH [46]</td>
<td>All except cardiac surgery (256)</td>
<td>1.17</td>
<td>0.78</td>
</tr>
<tr>
<td>Children with PH [71]</td>
<td>All types (192)</td>
<td>1.6</td>
<td>0</td>
</tr>
<tr>
<td>Children with PH [76]</td>
<td>All except cardiac bypass (284)</td>
<td>2.11</td>
<td>1.06</td>
</tr>
<tr>
<td>Children with PH [46]</td>
<td>Cardiac catheterization (141)</td>
<td>2.13</td>
<td>1.42</td>
</tr>
<tr>
<td>Children with PH [77]</td>
<td>Cardiac catheterization (70)</td>
<td>5.71</td>
<td>1.43</td>
</tr>
<tr>
<td>Children with PH [76]</td>
<td>Cardiac catheterization (168)</td>
<td>2.98</td>
<td>1.19</td>
</tr>
<tr>
<td>Children with PH [71]</td>
<td>Major surgery (20)</td>
<td>10</td>
<td>0</td>
</tr>
</tbody>
</table>
A pulmonary hypertensive crisis can be triggered by several stimuli that directly affect PVR or ventricular function (Box 28.6). The best-known stimuli of increased PVR are hypoxia and acidosis, as demonstrated by the classic work of Rudolph (Figure 28.6) [78]. Subsequent confirmatory investigations have shown that low alveolar oxygen tension (PAO$_2$) and respiratory acidosis due to hypercarbia are significant stimuli for pulmonary vasoconstriction (Figure 28.7) [79,80]. Noxious tracheal stimulation is another known trigger. Tracheal suctioning in the postoperative intensive care unit triggered a 70% increase in PVR and PAP in children with a history of PH [81]. Systemic hypotension caused by a decrease in SVR, stroke volume, or myocardial contractility can lead to inadequate coronary perfusion and right ventricular failure, thus triggering a pulmonary hypertensive crisis at another point in the cycle.

Treatment of a pulmonary hypertensive crisis is directed toward ameliorating the stimulating event and stabilizing hemodynamics (Table 28.4). Moderate hyperventilation with 100% oxygen, treatment of both respiratory and metabolic acidosis, and removal or attenuation of precipitating stimuli should be undertaken. A pulmonary vasodilator should be administered. Acute intravenous administration of pulmonary vasodilators can be associated with systemic hypotension, which may worsen coronary perfusion, so CCBs, sildenafil, and magnesium are generally not indicated for emergent treatment.
Figure 28.7 Mean pulmonary artery pressure (MPAP) is directly related to PaCO\(_2\). (Source: Morray et al. [80]. Reproduced with permission of Elsevier)

Table 28.4 Treatment of pulmonary hypertensive crisis

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administer 100% O(_2)</td>
<td>↑ PAO(_2) and PaO(_2) can ↓ PVR</td>
</tr>
<tr>
<td>Hyperventilate</td>
<td>PVR is directly related to PaCO(_2)</td>
</tr>
<tr>
<td>Exclude pneumothorax</td>
<td>Optimize ventilation</td>
</tr>
<tr>
<td>↓ mean airway pressure</td>
<td>Avoid P(<em>{alv}) &gt; P(</em>{art})</td>
</tr>
<tr>
<td>Correct metabolic acidosis</td>
<td>PVR is directly related to H(^+) level</td>
</tr>
<tr>
<td>Administer pulmonary vasodilators</td>
<td>iNO</td>
</tr>
<tr>
<td>Support cardiac output</td>
<td>Adequate preload and inotropic support, ECMO</td>
</tr>
<tr>
<td>Support coronary perfusion</td>
<td>Maintain SVR with epinephrine or NE</td>
</tr>
<tr>
<td>Analgesia</td>
<td>Decrease sensory/sympathetic mediated ↓ PVR</td>
</tr>
</tbody>
</table>

PAO\(_2\), alveolar oxygen pressure; PaO\(_2\), arterial oxygen pressure; PVR, pulmonary vascular resistance; PaCO\(_2\), arterial carbon dioxide pressure; P\(_{alv}\), alveolar pressure; P\(_{art}\), arterial pressure; H\(^+\), hydrogen ion; iNO, inhaled nitric oxide; ECMO, extracorporeal membrane oxygenation; SVR, systemic vascular resistance; NE, norepinephrine.

Furthermore, pulmonary hypertensive crises have been observed to follow initiation of treatment of PAH with intravenous prostacyclin analogs. Therefore, it is preferable in an urgent setting to administer pulmonary vasodilators by inhalation. This reduces the risk of systemic hypotension and coronary hypoperfusion by delivering the drug to the target pulmonary vasculature. The standard for inhaled pulmonary vasodilators is iNO, but inhaled prostacyclin analogs may also be effective in this setting [57].

Early treatment of bradycardia with atropine or another chronotropic drug can be helpful. If systemic hypotension persists following administration of pulmonary vasodilators, inotropic support is indicated. As isoproterenol, dobutamine, and milrinone can decrease SVR, and dopamine can increase the PVR/SVR ratio [82], many clinicians prefer epinephrine or norepinephrine for inotropic support during emergent treatment of a pulmonary hypertensive crisis, as these will generally increase SVR and decrease PVR, thus decreasing the PVR/SVR ratio [83,84].

In addition to inotropic support, a systemic vasopressor can improve coronary perfusion and ventricular function by supporting SVR and may avert cardiac arrest. For this purpose, epinephrine or norepinephrine, because they increase SVR while decreasing PVR [83,84], may be preferable to phenylephrine, which is both a pulmonary and a systemic vasoconstrictor [85,86]. Limited clinical reports suggest that arginine vasopressin and its synthetic analog, terlipressin, may increase SVR but not PVR in PAH patients [87,88].

Once the cycle of increased PVR and decreased ventricular function begins, however, cardiac arrest may be difficult to prevent. If cardiac arrest occurs, Pediatric Advanced Life Support guidelines for cardiopulmonary resuscitation should be followed [89]. Cardiac arrest associated with a pulmonary hypertensive crisis can be difficult to treat, and emergent use of ECMO may be necessary [90]. If emergent ECMO is required, improved outcomes are associated with shorter duration of cardiopulmonary resuscitation prior to ECMO [91], so an institutional protocol that anticipates the need for emergent ECMO in these situations is desirable.

**KEY POINTS: PREOPERATIVE RISK CONDITIONS**

- Children with PH are at increased risk of cardiac arrest and death under anesthesia. Those with supra-systemic PH are at greatest risk.
- Acute pulmonary hypertensive crises can occur in children with PH and are life-threatening.

**Anesthetic management**

Anesthetic management of the child with PH requires thoughtful preparation regarding the choice of anesthetic drugs, airway management, avoidance of triggering stimuli, prophylactic pulmonary vasodilators, and appropriate monitoring (Box 28.7).
Hemodynamic effects of anesthetic drugs

The ideal anesthetic drug for children with PH would have pulmonary vasodilating effects, would not depress cardiac contractility, would maintain SVR and cardiac output, and would be short-lasting and easy to titrate. Such an anesthetic agent, unfortunately, does not exist. Most anesthetics are associated with undesirable hemodynamic effects – depending on dose and speed of administration – by altering heart rate or rhythm, cardiac contractility, SVR, or PVR. The cardiovascular effects of anesthetic drugs are discussed in detail in Chapter 6, but the effects pertinent to a discussion of PH are summarized in Table 28.5 and as follows.

Volatile anesthetics. These cause a dose-dependent depression of cardiac contractility and a decrease of SVR [92,93]. These generally undesired effects are usually manageable during anesthesia for children with PH, when it is appreciated that they vary among the volatile anesthetics and are dose-dependent. Halothane causes greater depression of contractility than the newer anesthetics, while isoflurane and halothane cause a greater decrease of SVR. Furthermore, there is evidence that the volatile anesthetics are associated with a decrease in PVR. They attenuate hypoxic pulmonary vasoconstriction during one lung ventilation [94], and Qp:Qs remains unchanged in children with cardiac sepsal defects in response to halothane, sevoflurane, and isoflurane [95]. Thus, judicious use of volatile anesthetics is an important part of a balanced anesthetic in children with PH.

Propofol. Propofol causes dose-dependent depression of cardiac contractility [96]. In both adults and children with cardiac disease, propofol is associated with a marked decrease in SVR and MAP and a slight decrease in PVR and PAP [97,98]. In adults with artificial hearts, propofol causes vasodilation of systemic resistance and capacitance vessels and a decrease in PAP [99]. The hypotension associated with propofol can lead to decreased coronary perfusion of the hypertrophic right ventricle, so propofol should be used with caution in children with PH.

Ketamine. While ketamine is quite supportive of hemodynamic stability and is frequently recommended as an anesthetic of choice in patients with cardiovascular impairment or instability, its use in patients with PH is debated because of conflicting results of studies conducted under a variety of conditions (spontaneous or controlled ventilation, natural airway or endotracheal tube, room air or added oxygen) [100]. A marked increase in PAP and PVR has been observed during ketamine anesthesia in children with PAH breathing room air through a natural airway [101–103]. On the other hand, no change in PAP or PVR has been observed in response to ketamine in children with PAH during controlled ventilation or while receiving a pulmonary vasodilator, such as oxygen or sevoflurane [104,105]. Judgment doses of ketamine, therefore, may have a place in a balanced anesthetic for children with PH.

Etomidate. This is known to support systemic hemodynamics in children undergoing cardiac catheterization [106,107], but studies of its effect on pulmonary hemodynamics are rare. A study of adults with cardiac disease demonstrated minimal effects on PAP [108], while a pediatric study demonstrated a 28% increase in PVR [107].

Dexmedetomidine. This is associated with acutely decreased heart rate and increased MAP and SVR [109–111], followed over time by a slightly lower but generally stable MAP. These changes appear to be dose-dependent. Despite the early significant increase in SVR, a pulmonary vasoconstrictor response was not observed in children with PH who were chronically treated with pulmonary vasodilators [111]. Information regarding dexmedetomidine use in children with severe, untreated, or unstable PH is lacking.

Opioids. These can be associated with a decrease heart rate but otherwise have minimal hemodynamic effects. PVR remains unchanged in response to fentanyl [112], and pulmonary vascular responses to remifentanil are clinically insignificant in adults with artificial hearts [113]. Furthermore, the increase of PVR in response to noxious stimulation can be prevented by moderately large doses of fentanyl [81]. The opioids, particularly fentanyl and remifentanil, are an important part of the anesthetic management of children with PH.

Midazolam. Midazolam is associated with minimal hemodynamic effects and exerts clinically insignificant effects on the pulmonary vasculature of adults with cardiac disease [114]. Midazolam’s sedative and amnestic effects make it an important component of a balanced anesthetic in children with PH.

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**Table 28.5 Expected hemodynamic effects of anesthetic drugs**

<table>
<thead>
<tr>
<th>Anesthetic</th>
<th>Contractility</th>
<th>MAP</th>
<th>SVR</th>
<th>PAP</th>
<th>PVR</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Halothane</td>
<td>↓↓↓↓↓↓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isoflurane</td>
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MAP, mean arterial pressure; SVR, systemic vascular resistance; PAP, pulmonary artery pressure; PVR, pulmonary vascular resistance; HR, heart rate; ↓, decrease; ↑, increase; →, no significant change.

*aKetamine can depress contractility in vitro and in catecholamine-depleted patients.

*bDexmedetomidine can increase MAP during loading dose administration.
In order to minimize the undesired hemodynamic effects of a full anesthetic dose of a single anesthetic drug, it is preferable to utilize a balanced anesthetic technique. Balanced administration of sub-anesthetic doses of several anesthetics can achieve an adequate depth of anesthesia without the marked hemodynamic changes that can be associated with a high dose of a single drug. The authors generally employ midazolam, fentanyl or remifentanil, and sevoflurane or isoflurane for most procedures. High doses of fentanyl can be used for major operations if post-operative tracheal extubation is not anticipated. Judicious use of propofol in low infusion rates can be considered, but its administration should be undertaken with caution because its depression of SVR is not short-lived. The roles of ketamine and dexmedetomidine are less clear, but low to moderate doses have been used successfully.

Sometimes systemic hypotension can be observed despite a balanced technique, especially in children who are hypovolemic. In children with hypertrophic right ventricles, hypotension can lead to decreased coronary perfusion and acute right ventricular failure. Judicious use of a vasoconstrictor such as epinephrine or norepinephrine, therefore, is often recommended when hypotension is encountered intraoperatively.

**Perioperative pulmonary vasodilators**

In addition to administration of a balanced anesthetic technique and the avoidance of triggering stimuli, the risk of intraoperative cardiac arrest can be reduced by preoperative treatment with pulmonary vasodilator therapy. The odds ratio for children with PH to develop a major perioperative complication was only 0.31 in those who were chronically treated with a pulmonary vasodilator preoperatively [71]. When providing anesthetic care for non-cardiac surgery to children with severe PH (systemic or supra-systemic) or those not treated with chronic pulmonary vasodilator therapy, the authors administer iNO perioperatively from induction of anesthesia through recovery. The iNO is delivered at a dose of 20–40 ppm through the inspiratory limb of the breathing circuit; postoperatively, it can be administered via face mask or nasal cannulae [115] and weaned in the post-anesthesia care unit.

The authors favor perioperative iNO over other pulmonary vasodilators for this purpose because it delivers drug selectively to the pulmonary vascular bed, thus avoiding the systemic hypotension that can occur with acute intravenous or oral administration of non-selective pulmonary vasodilators. Indeed, trials of preoperative systemic administration of prophylactic pulmonary vasodilators to patients with PAH have been disappointing. When compared with placebo in children undergoing cardiac surgery, preoperative oral sildenafil was associated with worse postoperative ventricular function and no difference in PVR [116]. Similarly, adults who received oral sildenafil and beraprost preoperatively had lower SVR, greater vasopressor requirement, and no difference in PVR when compared with those who received a placebo [117].

In addition to iNO, other pulmonary vasodilators that have been shown to be effective when administered selectively by inhalation include the prostacyclin analogs epoprostenol [118], iloprost [119], and treprostinil [58]; the phosphodiesterase inhibitor milrinone [120]; and nitroglycerin [120]. Although perioperative studies are limited at this time, some of these may emerge as satisfactory prophylactic perioperative drug therapy for children with PH.

One caveat regarding pulmonary vasodilator therapy is that in patients whose PH is caused by pulmonary venous obstruction (group 2.4 of the 2013 Nice Pulmonary Hypertension Classification), administration of a pulmonary vasodilator can dilate the pulmonary arteries without relieving the obstruction to flow, thereby causing acute pulmonary edema and clinical deterioration. Another caveat regarding iNO use is that rebound PH following weaning of iNO can occasionally occur, especially after prolonged administration or a severe pulmonary hypertensive episode, and may require treatment with another vasodilator to facilitate weaning [121,122].

**Airway and ventilation management**

Airway management techniques by the anesthesiologist are chosen as appropriate for the surgical procedure. Although case reports have described pulmonary hypertensive crises in association with tracheal intubation [123,124], the reports suggest either that the patients were inadequately anesthetized or that the intubation occurred after hemodynamic deterioration had begun. When used alone, intravenous fentanyl 25 μg/kg will attenuate the significant increase in PAP and PVR in response to tracheal suctioning or intubation in children with PH [81,123]. In the authors’ experience, a balanced general anesthetic employing remifentanil or a lower dose of fentanyl as a component will achieve the same goal. Addition of topical laryngotracheal anesthesia with 2–4% lidocaine (limiting total dose to 3–5 mg/kg) for short procedures of 1–2 hours’ duration or less is an effective strategy to minimize noxious tracheal stimulation associated with intubation or extubation. The incidence of complications in children with PH undergoing non-cardiac surgery or cardiac catheterization was found to be independent of the method of airway management (natural airway, laryngeal mask airway or endotracheal tube) [46,76]. Therefore, with adequate topical and general anesthesia, the authors do not hesitate to intubate the trachea when indicated for the surgical procedure or condition of the patient and believe that intubation provides the important benefit of control of the airway and ventilation.

Alternatively, airway management with a face mask, laryngeal mask airway, or the natural airway (with end-tidal CO₂ monitoring via nasal cannulae) can be employed when indicated and appropriate for the procedure. It should be remembered that hypoxia and hypercarbia can trigger a pulmonary hypertensive crisis and that airway obstruction or hypoventilation can occur during some sedative and anesthetic management.
techniques [125]. Thus, the anesthesiologist should consider all options for airway access and ventilatory management.

Ventilatory support should be provided as needed with the goals of maintaining appropriate lung volumes and blood gases. PVR is increased at both very small and very large lung volumes and is lowest at functional residual capacity (Figure 28.8) [126]. Prevention of atelectasis by keeping lung volumes above closing capacity and avoidance of excessive tidal volume are therefore both important. As PVR increases during alveolar hypoxia, hypoxemia, and acidosis, normal blood gases should be maintained with appropriate ventilatory and airway management.

**Monitoring**

American Society of Anesthesiologist guidelines for intraoperative monitoring are followed. Invasive monitors are used as appropriate for the patient’s status and planned procedure. Despite the known risks of pulmonary artery catheters, they provide valuable hemodynamic information, and limited evidence supports their use during major surgical procedures and intensive care of children with PH [127,128].

Echocardiography offers non-invasive assessment of patients with PH, and both transthoracic and transesophageal echocardiography have been utilized as intraoperative monitors. Estimation of right ventricular systolic pressure can be made by applying Bernoulli’s equation to measurement of the tricuspid valve regurgitant jet velocity (Figure 28.1, Box 28.3, Video 28.1). The extent of right ventricular dilation and right-to-left interventricular septal shift, as well as biventricular function, can be readily assessed subjectively (Figure 28.9; Videos 28.2 and 28.3). This is important, as greater right ventricular encroachment on left ventricular volume is associated with greater risk of perioperative adverse events in children with PH [76].

**Post-anesthesia recovery**

The high perioperative risk associated with PH continues during the post-anesthetic recovery period. Therapeutic or prophylactic drugs administered intraoperatively, such as iNO and oxygen, should be continued postoperatively and weaned gradually as the child awakens and remains stable. The possibility of rebound PH following weaning of iNO, especially after prolonged administration or a severe pulmonary hypertensive episode, should be kept in mind. All precautions should be taken to avoid hypoxemia, hypotension, and hypovolemia. Postoperative pain control should be effective. Following recovery from anesthesia, stable patients who have undergone minor procedures without complications can be discharged. Depending on the nature of the procedure, the severity of PH, the occurrence of adverse events, and the child’s condition, it is often advisable to admit the child overnight to a monitored bed where rapid medical response is possible.

**KEY POINTS: ANESTHETIC MANAGEMENT OF PH**

- There is no one ideal anesthetic agent for children with PH. It is essential to understand the different hemodynamic effects of anesthetic agents and adopt a balanced anesthetic technique.
Conclusions

Pulmonary hypertension is a common occurrence in patients with CHD, and although relatively less common, patients with idiopathic and inherited PH are usually cared for by congenital cardiac anesthesiologists. Recent advances in understanding of pathophysiology, classification, and medical therapy have led to increased survival in this population. Recent data about the increased risk of anesthesia in this population allow the anesthesiologist to appropriately create an anesthetic plan to minimize complications, and arrange for proper peri-anesthetic monitoring and rescue therapy where indicated.

Selected references

A full reference list for this chapter is available at:
http://www.wiley.com/go/andropoulos/congenitalheart


60 Barst RJ, Ivy DD, Gaitan G, et al. A randomized, double-blind, placebo-controlled, dose-ranging study of oral sildenafil citrate in treatment-naive children with pulmonary arterial hypertension. Circulation 2012;125:324–34. STARTS-1 and STARTS-2 (Sildenafil in Treatment-Naive Children With Pulmonary Arterial Hypertension Study) compared low-, medium- and high- dose sildenafil monotherapy and found the three doses had no significant difference in the primary outcome measure: percent change from baseline in peak oxygen consumption. Secondary measures of improved functional class and hemodynamics were found with the medium- and high-dose groups. However, there was increased mortality in these two groups. The European and United States drug authorities interpreted these data differently.

78 Rudolph AM, Yuan S. Response of the pulmonary vasculature to hypoxia and H+ ion concentration changes. J Clin Invest 1966;45:399–411. This classic paper described the relationship between pulmonary vascular resistance and hypoxia and acidosis.


CHAPTER 29
Anesthesia for the Cardiac Catheterization Laboratory

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Introduction to the cardiac catheterization laboratory
The objective of this chapter is to provide information of value to anesthesiologists asked to provide care for patients undergoing cardiac catheterization. The chapter is divided into four sections. The first deals with general issues relevant to all procedures conducted in the cardiac catheterization laboratory. The remaining three sections discuss issues specific to, in turn, diagnostic catheterizations, endovascular interventions, and electrophysiological studies. Much of what is discussed does not relate directly to the anesthesiologist’s own interventions. Rather, we have stressed the importance of a wider understanding of how the planned intervention fits into the management of the patient as a whole. Hence much emphasis is placed on the need for close cooperation with the interventional cardiologist, to ensure that information gained from diagnostic studies is truly reflective of the patient’s condition and to anticipate potential adverse effects of planned interventions. Individual interventional procedures are described, detailing not only how a procedure is performed, but also why. It is only by understanding such context that anesthesiologists can ensure that they themselves make valid decisions that add value to the care of the patient, especially on those occasions when events do not run to the preordained plan.

Recent trends and developments in cardiac catheterization
This is now the third edition of this textbook and this chapter. During this time, many of the trends identified in the first edition have continued; in particular, the growth in the number of interventional procedures and the replacement of diagnostic catheterizations with other imaging modalities. Newer trends can also be clearly identified and these will be discussed briefly here and in more detail later in the chapter. These changes have implications for the anesthesiologist. A particular trend has been an increase in the number of sicker, smaller patients with complex disease undergoing interventions with more profound physiological consequences. Despite this, many children presenting for cardiac catheterizations are relatively well and, when all goes according to plan, present no particular challenge to the anesthesiologist. Unfortunately, things do occasionally go wrong and a dilemma for clinical teams is how much effort and concentration of resources should be directed towards the anticipation of events which,
while statistically rare, are potentially disastrous. These dilemmas can be difficult even in well-funded healthcare systems, but raise serious practical and ethical concerns for providing treatment in locations in which resources are much more constrained.

Figure 29.1 shows the growth in the numbers of interventional catheterizations in the UK over the last 10 years [1]. Intervventional catheterizations in children have increased by 50%. More impressive is the apparent growth in interventional catheterizations in adult patients with congenital heart disease (CHD). There may have been changes in the pattern of reporting of these procedures; however, it is likely that the growing prevalence of CHD in adults, combined with newer procedures such as pulmonary valve implantation, has led to a substantial and real increase in the number of catheter interventions for CHD in adults.

A further trend has been the growth in endovascular palliative procedures in neonates, performed either using traditional endovascular approaches or as ‘hybrid’ procedures. This has come from the recognition of considerable morbidity, long-term disability, and mortality associated with surgical palliation for complex disease. In the UK there has been a substantial increase in mortality in neonates undergoing arterial (systemic arterial to pulmonary artery [PA]) shunt over the last 10 years, during a period when all case mortality for congenital heart surgery has fallen from 4.3% to 2.6% [1]. This increased mortality has almost certainly resulted from offering palliations to patients with increasing complex congenital lesions, of smaller size and with co-morbidities. Procedures such as stenting of the ductus arteriosus or the right ventricular outflow tract (RVOT) have evolved as valid alternatives to arterial shunts for selected patients. “Hybrid” procedures describe a number of procedures in which techniques traditionally confined to the catheterization suite are used during surgery (and vice versa). In the published literature this term is often synonymous with hybrid palliation of hypoplastic left heart syndrome (HLHS), a procedure that has evolved in recognition of high levels of morbidity in patients undergoing the Norwood stage I palliation procedure and high mortality in selected populations (such as very low-weight patients).

In previous editions, the need for an anesthesiologist to supervise children undergoing cardiac catheterization has been a subject of discussion. In countries with well-resourced healthcare, it would now be accepted that patients requiring suppression of consciousness to allow cardiac catheterization should do so under the supervision of an anesthesiologist. Debates about standards have moved on and the availability of surgical backup and facilities for mechanical support of the circulation are more topical discussions.

A further trend is that many children living in countries in which, a few years ago, treatment of their CHD was not available can now expect such treatment. In many of these countries there remains a massive unmet need. Physicians in these locations have a duty to make best use of the resources available, to allow treatment to be offered to the largest number of patients. Barriers to wider use include high cost of disposables and devices (an Amplatzer™ septal occluder [St. Jude Medical, St. Paul, MN, USA], atrial septal defect [ASD] device will cost roughly the same in the US and in India; two countries with very different health economies). Attempts to export standards developed for use in well-resourced countries to such settings can have unintended consequences and, in effect, deny life-saving treatment to patients. However, there are other standards that should not be considered negotiable. It would be the authors’ contention that the benefits of supervision of patients by a suitably experienced anesthesiologist outweigh the costs and should be a requirement whenever children undergo sedation or anesthesia for cardiac catheterization.
Environment
The layout and equipment of operating rooms have evolved over many years to provide access to the patient for both the surgeon and the anesthesiologist. This is not the case in the cardiac catheterization laboratories and many aspects of the environment are challenging [2]. Equipment will inevitably limit access to the patient once the procedure has begun, and even at the start, large immobile pieces of equipment will often obstruct the anesthesiologist trying to move around the patient (Figure 29.2). Issues such as lighting, temperature regulation and the patient moving can often be circumvented, with planning and good communication, especially if the team realizes their importance to good outcomes and efficient throughput. Warming devices, such as forced air warmers, will not affect the quality of imaging or the function of electronics, and adequate lighting to allow safe observation of the patient and perform procedures, such as placing an intravenous cannula, should be easy to provide. It is, however, necessary to move the table to allow imaging of different parts and, even with the most cooperative cardiologist, it is unlikely that warning will be given for every movement. Lines and tubes should be secured, positioned, and of sufficient length to allow for this.

When catheterization laboratories are being designed, it is important that anesthesiologists have input to this process. Working out how multiple pieces of equipment will move around the patient can be challenging and will require discussion between architects and clinical teams. It is equally important to consider how patients themselves will move in and out. The layout should be mindful of all eventualities, including the need for urgent surgical exploration. Accommodating the additional equipment for mechanical support of the circulation and moving of patients on such support can be a particular problem.

Catheterization laboratories are often placed some distance from operating rooms and facilities for recovery. When designing new facilities, this should be avoided and the catheterization laboratory, cardiac operating room, recovery facilities and intensive care should all be within a small radius. Where this is not possible, efforts are required to reduce any risk to the patient. There should be clear protocols for communicating with colleagues, in particular surgical teams. Some duplication of equipment and facilities (such as recovery facilities) will be necessary. Standards for such facilities should be equivalent to those for an operating room.

Newer hybrid suites are larger in size and contain equipment for both catheter interventions and surgery, including circulatory support backup with extracorporeal membrane oxygenation (ECMO) or standard cardiopulmonary bypass (CPB). If procedures requiring CPB or combined “hybrid” type procedures are planned then attention needs to be paid to air exchange, operating room standards, and appropriate numbers of gas, suction, and electrical outlets as well as anesthetic gas scavenging. Space for a heart–lung machine adjacent to the patient and not likely to be struck by a rotating C-arm is also a consideration.

A further recent development has been the use of magnetic resonance imaging (MRI) during cardiac catheterization [3–6]. The MRI scanner is usually in an adjacent room, and the catheterization laboratory bed is mounted on tracks to allow the patient to be moved...
back and forth directly into and out of the scanner, which is behind lead-lined automatic doors. Potentially this allows for a reduction in radiation dose to the patient and improved diagnostic information that can be obtained immediately before and after a catheter intervention. Cardiology equipment has been developed to allow transfer of the patient into strong magnetic fields. Anesthetic equipment compatible with MRI scanning has improved greatly in recent years and high-quality equipment should be available. Care should be taken when moving patients, equipment, and personnel into the MRI room. Full MRI precautions, including safety zones, MRI-compatible equipment, and trained personnel, are necessary to ensure safety. When not in use for catheterization cases, the MRI scanner can be used for diagnostic cardiac MRI scans, with a separate entrance into the scanning room.

Radiation exposure of both the patient and staff is a hazard during cardiac catheterization. The risk of injury is increased with larger dose (amount of energy absorbed); however, the magnitude of effect is not dose-related. Exposure is measured in rem or sieverts (1 rem = 1 mSv). Background exposure in the UK is 2.7 rem/year and this increases to 7.8 rem/year in areas with high natural levels of radon gas. The risk of a fatal cancer is increased by 0.04% per rem of lifetime exposure and no level of radiation exposure can be considered safe [7]. In a pediatric study evaluating exposure during both diagnostic and therapeutic procedures, average doses were 4.6 and 6 rem, respectively [8], and younger patients tended to have higher exposures. In a 2006 study examining chromosomal damage in patients with CHD, there was clear evidence that cardiac catheterization was associated with long-term chromosomal damage [9].

Staff are also exposed to radiation and staff in catheterization facilities have been identified as having higher exposures [10]. The maximum radiation exposure recommended for medical workers is 5 rem/year. Ideally, exposure should be much lower than this (0.12 rem/year). Dose limitation relies on time, distance, and barriers. Radiation dose is reduced with distance from the source according to the inverse square law. Barriers include protective clothing (“lead” aprons, thyroid collar, and protective eye glasses) and “plexiglas” screens. The threshold for cataracts may be reached in a few years without appropriate protection [11].

Anesthetic considerations

Unlike open surgery, procedures in the catheterization laboratory are, on the whole, not associated with substantial stress or inflammatory responses, large fluid shifts, or severe postoperative pain. Many procedures can be conducted on a day-case basis and most (but not all and not predictably) of the intraoperative painful stimuli occur during the first part of the procedure. However, the patients presenting can at times have very severe underlying illness and life-threatening adverse events do occur, which require effective and prompt action from the anesthesiologist [12,13].

Subjects of controversy have been as follows: is any suppression of consciousness required during cardiac catheterization; if consciousness is suppressed, to what level should it be suppressed; and who should be administering and monitoring the sedation and its consequences? Adults commonly undergo cardiac catheterization without the use of systemic pharmaceuticals to suppress consciousness. However, cardiac catheterization for children often involves complex interventions, procedures can be prolonged and it is unlikely that the majority of children will tolerate this whilst awake. “Lighter” levels of sedation, which allow for continuing communication with the patient or which aim for normal sleep, will be unlikely to ensure cooperation during painful or prolonged procedures. In addition, such approaches may be counterproductive by eliminating the ability of older children to cooperate. Hence levels of sedation are likely to be required that ensure the patient will remain still for long periods of time and not respond to occasional painful stimuli. Achieving this without the risk of loss of normal airway reflexes can be unreliable. Some authorities have made a distinction between such “deep sedation” and anesthesia. Such distinctions are largely arbitrary and in guidelines published in the UK such a distinction has not been made [13,14]. The choice of agents to provide such sedation is of less importance than the level of sedation achieved. Perceptions that agents administered by oral or intramuscular routes are safer in this respect than inhaled or intravenous agents are erroneous. The longer action and onset time of such agents probably increase, rather than reduce, the risks associated with their use.

One reason for making a distinction between anesthesia and “deep sedation” is that anesthetics are administered under the supervision of an anesthesiologist, whilst sedation is frequently not. Lack of anesthetic personnel may mean that deep sedation supervised by a non-anesthesiologist is seen as preferable over no sedation. This situation does not provide optimum care for children [15]. A recent audit of over 1,500 patients showed that airway-related issues were the main adverse events associated with sedation techniques [16]. Guidelines published by the American Society of Anesthesiologists (ASA) have stated that any provider of sedation should be able to rescue the patient should the level of sedation be deeper than intended [17]. It follows that the provider of sedation should have a sound knowledge of the pharmacology of the drugs being used and how it is affected by the underlying disease process; knowledge of the procedure being performed; and an ability to conduct procedures, including advanced airway management and intravenous access, in a wide range of patients. In the UK, all children undergoing cardiac catheterization will do so under the supervision of an anesthesiologist. Most commonly they will receive a general anesthetic with appropriate measures to control the airway. Irrespective of the provider and the technique chosen, assessment and monitoring of patients undergoing cardiac catheterization should
be comparable to that of a patient undergoing any other operative procedure [18].

A number of techniques can be employed to provide anesthesia or sedation during cardiac catheterization and it is difficult to suggest any one technique as optimal. Rather, the perioperative plan should be adapted to the best interest of the child given their condition and the purpose of the proposed procedure. Given this, consistency in the approach will be of benefit, in particular when interpreting physiological findings. Endotracheal intubation is indicated when the child is at risk of ventilatory failure due to illness or prematurity; transesophageal echocardiography (TEE) is to be used; interventions are likely to be prolonged; significant hemodynamic disturbance is anticipated; there is risk of sudden movement at crucial points during interventions (e.g. coughing during a PA intervention); or there is risk of hemoptysis. In other cases, the pros and cons should be considered. For example, in a patient undergoing a cardiac catheterization to assess their suitability for a Fontan procedure, positive pressure ventilation will affect measurement of pulmonary artery pressure (PAP), a key objective of the procedure. Use of intravenous agents (including ketamine and propofol) can avoid the need for intubation in selected patients. In all cases, monitoring of the adequacy of the airway and ventilation is required. This may be aided by specially adapted nasal cannulas or masks. Laryngeal mask airways can allow for “hands free” anesthesia and allow for spontaneous or assisted ventilation using inhaled or intravenous agents.

Local anesthetic techniques can be used (in some cases) as an alternative to general anesthesia or in combination with general anesthesia or sedation. Infiltration of local anesthetics at vascular access sites is simple and, if performed correctly, should not complicate subsequent access. Toxicity due to lidocaine has been described during cardiac catheterization, but only in association with massive overdose [19]. Central neuraxial blockade may be considered if access is to be confined to the groin. Caudal anesthesia is associated with almost no hemodynamic changes in infants and may avoid the need for sedation [20]. However, the need for heparin during the procedure is a consideration. Use of topical local anesthetics has been reported, but it was not found to be useful in reducing the need for sedation or in reducing hemodynamic changes [21].

Patients with CHD and their parents are often understandably anxious when presenting for a procedure. There are benefits from premedication even with parental presence at induction of anesthesia [22]. Midazolam 0.5–0.75 mg/kg is a safe and effective oral premedication for children with CHD and has the advantage of a rapid onset [23,24]. The most common sequelae of cardiac surgery for CHD are arrhythmias and myocardial dysfunction. Recurrent laryngeal and phrenic nerve palsy are recognized complications of cardiac surgery and result in limited respiratory reserve, as does congestive heart failure. Feeding difficulties and gastroesophageal reflux are also common. In addition, 25% of children with CHD have other congenital anomalies. Craniofacial, airway, and intrathoracic anomalies are a major cause for concern. The combination of a patient with a challenging airway, limited cardiac reserve, and difficult vascular access in an area of the hospital often some distance from colleagues epitomizes the challenge for the pediatric anesthesiologist in the cardiac catheterization laboratory.

Complications

There have been several reports on the incidence of complications in the catheterization suite. Overall incidence has been reported at between 7% and 24%, with therapeutic interventions having a higher complication rate than solely diagnostic catheterization (11.6% vs. 9.3%) [25]. Mortality rates from various reports have been < 1% [16,25,26]. Dysrhythmias and vascular damage are the two most commonly encountered serious complications. Other serious complications include bleeding, perforation or rupture of vessels of the heart, cardiac tamponade, vascular thrombosis, air embolus, catheter fragment embolus, valvular incompetence, allergy to contrast medium or drugs, stroke, and brachial plexus injury [27]. Risk factors for complications are patient age under 1 year, smaller size and the particular intervention performed [25]. Severe pulmonary hypertension has a significant risk of mortality [28,29]. In reports to the Pediatric Perioperative Cardiac Arrest Registry, children with CHD and children undergoing cardiac catheterization feature commonly [12]. Risk factors are similar to those described above and include young age, single-ventricle pathology and patients presenting prior to surgical repair. The need for facilities to rapidly deploy mechanical support of the circulation should be considered; although even among units with such facilities, the real time to institution of support will vary greatly.

Arrhythmias are common and usually transient. Contributory factors such as electrolyte disturbance, hypercarbia, and excessive catheter manipulation within the heart should be minimized. Pacing can be instituted to treat heart block or supraventricular tachycardia (SVT) and equipment for defibrillation must be immediately available. Other causes of arrhythmia should be considered, including cardiac ischemia, drugs, coronary air emboli, or direct damage to the myocardium or conducting system.

Catheterizations used for interventional procedures have a larger diameter than those used during diagnostic studies, and the risk of vascular damage at the site of insertion is increased, as is the risk of damage to heart structures. Rare complications, such as perforation of the heart or vessels or valvular incompetence, may require urgent surgical intervention. Blood should be immediately available and interventional procedures (except for balloon septostomy) in children should only be conducted in hospitals where there are facilities for cardiac surgery [7,30,31]. In the event of sudden blood loss, rapid transfusion and arterial monitoring are possible via vascular access sheaths placed for the catheterization.
the event of rupture or dissection of blood vessels during balloon angioplasty, it may be possible for the cardiologist to tamponade the rupture by reinfusion of the balloon; however, emergency surgical repair will often be required. Pericardial tamponade may occur from perforation of the heart; emergency pericardiocentesis with reinfusion of the withdrawn blood into the femoral sheath may be life-saving while the surgical team is mobilized.

Thrombosis and thromboembolization may occur at any site where the vascular endothelium is disrupted. Heparin is given in a dose of 50–150 units/kg after arterial cannulation, when the systemic circulation is entered, and during procedures that inevitably cause damage to the vascular endothelium. Protamine may be used to reverse the effects of heparin but is not routinely required.

Governance, measurement of quality, and safety initiatives

It has become an accepted part of clinical practice that physicians continually monitor outcomes within their practice. Reporting and benchmarking of mortality outcomes for heart surgery and for interventional procedures have become a part of this [1]. However, mortality is generally less than 1% for cardiac catheterizations in patients with CHD, and is therefore a crude marker of performance. Other quality indicators can include other outcomes (such as incidence of heart block), procedural indicators (such as the number of cases performed) and near misses which should also be reported and discussed by the team. It is important that anesthesiologists take part in such initiatives and that adverse events and near misses related to anesthesia and sedation are also discussed.

The World Health Organization has promoted the use of checklists to improve patient safety. Such lists can be used during cardiac catheterization with the aim of reducing adverse events and improving communication within the team. Among other issues, patients at high risk of requiring surgical interventions or mechanical support should be identified and lines of communication with surgical teams should be clear. The team should, at intervals, practice their response to unusual severe adverse events.

Diagnostic catheterization

The information required for the correct treatment of CHD includes data as to the morphology of abnormalities and the patient’s physiology. Erroneous data can lead to the patient receiving inappropriate treatment. At worst, this can mean the patient having surgical procedures from which they have little hope of survival, or being denied potentially life-saving therapy. Diagnostic catheterization is one of several modalities used in the investigation of CHD. While no longer required for the majority of patients presenting for surgery, it remains an important investigation in specific situations. These situations include the most marginal and vulnerable patients in whom decision-making can be the most difficult and in whom accurate data are most important. Anesthesia and sedation will not affect the morphology of the condition, but can have profound effects on the physiology. The anesthesiologist and cardiologist should be aware of this and work together to achieve the best possible data to support decision-making.

Advances in other imaging techniques, most notably echocardiography and MRI, coupled with the invasive nature of cardiac catheterization and radiation exposure, mean that careful consideration is given to the indications for diagnostic catheterization. The American Heart Association in 2011 produced recommendations on indications for diagnostic catheterization [32] which encompass the following indications:

• To measure central and peripheral intravascular pressures and derive hemodynamic information, such as pulmonary vascular resistance (PVR) and systemic vascular resistance (SVR), shunt fractions and cardiac output (see Tables 29.1 and 29.2). The most common situation for this type of investigation is in preparation for the Fontan procedure.
• To define cardiac and vascular anatomy: poor windows can defeat the most expert echocardiographer and

KEY POINTS: THE CARDIAC CATHETERIZATION LABORATORY

• The cardiac catheterization laboratory is a challenging environment, often distant from the operating room complex, posing multiple challenges for the anesthesiologist.
• There needs to be close cooperation between the anesthesiologist and the interventional cardiologist to obtain the best result for the patient.
• Intervenional procedures should (with the possible exception of balloon atrial septostomy) be performed only in hospitals with facilities for surgical exploration, including institution of mechanical support of the circulation.
• The practitioner caring for children requiring suppression of consciousness during cardiac catheterization should have skills in managing predictable and unpredictable effects of sedation and adverse events related to the catheterization procedure.
• Dysrhythmias and vascular complications are the two most commonly encountered adverse events.
• Regular simulation to practice management of serious adverse events should occur.
Table 29.1 Normal cardiac catheterization data

<table>
<thead>
<tr>
<th>Pressure (mmHg)</th>
<th>Oxygen saturation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Newborns</td>
</tr>
<tr>
<td>Right atrium</td>
<td>60–80</td>
</tr>
<tr>
<td>a wave</td>
<td>3–8</td>
</tr>
<tr>
<td>v wave</td>
<td>2–6</td>
</tr>
<tr>
<td>Mean</td>
<td>0–4</td>
</tr>
<tr>
<td>Right ventricle</td>
<td>65–75</td>
</tr>
<tr>
<td>Systolic</td>
<td>65–80</td>
</tr>
<tr>
<td>End diastolic</td>
<td>2–7</td>
</tr>
<tr>
<td>Pulmonary artery</td>
<td>65–75</td>
</tr>
<tr>
<td>Systolic</td>
<td>65–80</td>
</tr>
<tr>
<td>Diastolic</td>
<td>35–50</td>
</tr>
<tr>
<td>Mean</td>
<td>40–70</td>
</tr>
<tr>
<td>PA wedge</td>
<td></td>
</tr>
<tr>
<td>a wave</td>
<td>6–10</td>
</tr>
<tr>
<td>v wave</td>
<td>7–11</td>
</tr>
<tr>
<td>Mean</td>
<td>5–8</td>
</tr>
<tr>
<td>Left atrium</td>
<td>95–100</td>
</tr>
<tr>
<td>a wave</td>
<td>4–7</td>
</tr>
<tr>
<td>v wave</td>
<td>6–12</td>
</tr>
<tr>
<td>Mean</td>
<td>3–6</td>
</tr>
<tr>
<td>Left ventricle</td>
<td>95–100</td>
</tr>
<tr>
<td>Systolic</td>
<td>65–80</td>
</tr>
<tr>
<td>End diastolic</td>
<td>3–7</td>
</tr>
<tr>
<td>Aorta</td>
<td>95–100</td>
</tr>
<tr>
<td>Systolic</td>
<td>65–80</td>
</tr>
<tr>
<td>Diastolic</td>
<td>45–60</td>
</tr>
<tr>
<td>Mean</td>
<td>55–65</td>
</tr>
<tr>
<td>Flows</td>
<td></td>
</tr>
<tr>
<td>Pulmonary (Qp)</td>
<td>3.5–5.0</td>
</tr>
<tr>
<td>Systemic (Qs)</td>
<td>3.5–5.0</td>
</tr>
<tr>
<td>Resistances</td>
<td></td>
</tr>
<tr>
<td>Pulmonary (Rp)</td>
<td>8–10</td>
</tr>
<tr>
<td>Systemic (Rs)</td>
<td>10–15</td>
</tr>
</tbody>
</table>

BSA, body surface area; PA, pulmonary artery.

certain anatomical features are difficult to visualize. This occurs in a minority of cases and usually implies either complex anatomy or complicating factors in the patient, such as lung disease. Similar anatomical data can often also be obtained by MRI and computed tomography.

- To evaluate myocardial function and to assess the effects of drugs and respiratory interventions on the cardiovascular system, such as is performed during investigation of patients with pulmonary hypertension.

- Endocardial biopsies, coronary artery angiography, and assessment of myocardial function are part of the routine surveillance of patients following heart transplantation. Endocardial biopsy is also used in the diagnosis of cardiomyopathy and viral myocarditis.

- Diagnostic studies are also an integral part of transcatheter interventional procedures.

Procedure

The routine approach to diagnostic catheterization in patients with biventricular hearts is via the femoral vein using the Seldinger technique. Access to the internal jugular or subclavian vein is required to evaluate the pulmonary arteries following cavopulmonary connections or hemi-Fontan procedures. If necessary, the femoral artery is also accessed using a similar technique. After dilatation and placement of an appropriate sheath, catheters are advanced through the circulation, and pressure and oxygen saturation measurements are made in sequence. Appropriate oxygen saturation measurements will allow the detection of shunts, and calculations of shunt fraction in combination with measurements or estimates of oxygen consumption will allow calculation of cardiac output and pulmonary blood flow (see Tables 29.1 and 29.2 for normal data and calculations). The use of high-inspired
Hemodynamic calculations performed during cardiac catheterization

\[
\begin{align*}
\text{Pulmonary: } Q_p &= \frac{V O_2}{(S_O_2 - S_HbO_2) \times Hgb \times 1.34 \times 10} \\
\text{Systemic: } Q_s &= \frac{V O_2}{(S_O_2 - S_HbO_2) \times Hgb \times 1.34 \times 10} \\
\text{Effective pulmonary: } Q_{ep} &= \frac{V O_2}{(S_O_2 - S_HbO_2) \times Hgb \times 1.34 \times 10}
\end{align*}
\]

Resistances

\[
\begin{align*}
\text{Pulmonary: } R_p &= \frac{P_{AOP} - P_{LAP}}{Q_p} \\
\text{Systemic: } R_s &= \frac{P_{SAO} - P_{LAP}}{Q_s}
\end{align*}
\]

Shunts

\[
\begin{align*}
\text{Pulmonary to systemic: } Q_p/Q_s &= \frac{S_O_2 - S_HbO_2}{S_O_2 - S_HbO_2} \\
\text{Left to right: } Q_p - Q_{ep} &\quad (\text{absolute flow}) \\
\text{Right to left: } Q_p - Q_{ep} &\quad (\text{absolute flow})
\end{align*}
\]

AO, Aorta; AOP, Aortic pressure; LAP, Left atrial pressure; MV, mixed venous; PA, pulmonary artery; PAP, pulmonary artery pressure; PV, pulmonary vein; Qap, effective pulmonary flow; Qp, pulmonary flow; Qs, systemic flow; RAP, right atrial pressure; Rpv, pulmonary vascular resistance; Rs, systemic vascular resistance; S, saturation; VO2, oxygen consumption

Anesthetic considerations

Many of the anesthetic considerations for diagnostic catheterization are similar to those discussed earlier. In comparison with interventional procedures, diagnostic catheterizations are quicker and serious complications are less common [24]. However, patients are not infrequently smaller and sicker. The objective of the procedure is to gather information and it should be realized that the implication for the child’s future could be great. Anesthesia can have profound effects on physiological measurements made during the procedure and on subsequent decision-making.

Unlike anatomy, physiology is in a continuous state of change. A patient’s blood pressure will decrease when they sleep or relax, and increase during exercise, or when they have it measured during a medical examination. Any measurement represents the variable measured only at that point of time and under the conditions in which it is measured. State of wakefulness, emotional affect, states of hydration, body position, and recent diet can all affect the patient’s hemodynamics. As a rule, measurements should be interpreted within the context in which they are taken and important medical decisions should not be made on the basis of a single measurement. This latter principle is a difficulty when measurements are made during invasive procedures. Decisions should rarely be made on the basis of a change in a single pressure of 1 or 2 mmHg. Collaborating evidence should be sought, and catheter data greatly at odds with the patient’s clinical condition, or other data (e.g., from echocardiography), should be viewed with suspicion. Although not ideal, it is better to repeat a catheterization than to make a decision on the basis of erroneous information.

All sedative and anesthetic medications will influence hemodynamics. The hemodynamic effects of most agents have been well described in Chapter 6 and specific agents are discussed below in relation to cardiac catheterization and CHD. In addition, both respiratory depression and measures taken to prevent or relieve respiratory depression will affect measurements. Care and selection of agents can reduce, but not eliminate, these effects and it is important that the anesthesiologist and cardiologist have an understanding of these effects in order to interpret the data correctly. The most obvious hemodynamic effects will be on systemic blood pressure, arterial oxygen saturation, and carbon dioxide concentration. Other variables will also be important, including vascular resistances, cardiac output, oxygen consumption and pulmonary-to-systemic-blood flow ratio (Qp:Qs).

Maintaining a near-normal blood pressure can be challenging. Modest reductions in blood pressure are normal during anesthesia. Most sedative agents will cause a direct reduction in SVR and reduction in cardiac output can result from negative inotropic or chronotropic effects of agents, or from reduced preload (due to lowered venous tone or positive intrathoracic pressure). These effects will tend to be greater in sicker patients, in whom accurate information is likely to be of greatest benefit. Excessive dosing of
agents should be avoided. Judicious boluses of intravenous fluid may be required. Vasopressors should usually only be given after discussion with the cardiologist, unless they are being given to prevent immediate harm to the patient. Of note, when interpreting data, it must be remembered that cardiac output will also fall under general anesthesia due to a reduction in body oxygen consumption.

Respiratory manipulations will affect hemodynamics. In one study, a change from positive to negative pressure (cuirass) ventilation increased cardiac output by 11% in healthy children, 28% in postoperative cardiac patients, and 54% in patients with a Fontan circulation [37,38]. A similar increase in cardiac output has been demonstrated on extubation of postoperative Fontan patients [39]. If the child has a large left-to-right shunt, the effects of breathing high concentrations of oxygen are twofold: first, it is necessary to consider the contribution of dissolved oxygen when calculating pulmonary blood flow using the Fick equation; and secondly, the high oxygen levels will likely decrease PVR and increase the Qp:Qs ratio. Similarly, changes in arterial carbon dioxide tension or pH will affect pulmonary blood flow. Small changes in pulmonary vein oxygen saturation make large changes in calculation of shunt fraction.

Anesthetic techniques vary. In the UK, almost all catheterizations are performed with general anesthesia and endotracheal intubation [40]. In North America, sedation and anesthetic techniques without control of the airway or ventilation are more common. The pros and cons of these two approaches are multiple. As detailed earlier, positive pressure ventilation has definite, but largely predictable, effects on hemodynamics. These effects can be avoided by allowing for spontaneous ventilation, and the perfect situation would be a patient spontaneously breathing room air, with a patent airway and a normal respiratory drive. This cannot, however, be reliably achieved in all patients. Whether such changes are of sufficient magnitude to lead to an erroneous course of management is unclear, but for most patients this is unlikely. The advantage of techniques allowing spontaneous breathing should be weighed against the risk of airway obstruction, hypercapnia, or atelectasis, both risking more profoundly misleading data [41]. Patients at higher risk of respiratory compromise or airway obstruction should generally have a controlled airway during catheterization. Otherwise it is probably more important to have a consistent institutional approach than the specific nature of this strategy. There are strong arguments that whatever technique is being used, a pediatric anesthesiologist should be in charge of the patient [14].

**Choice of anesthetic/sedative medications**

The effects of sedative and analgesic drugs on the heart are variable. Inhalational anesthetics cause peripheral vasodilatation, varying degrees of myocardial depression, and have effects on sinus node function and cardiac conduction tissue. Sevoflurane is the most commonly used inhalational agent in developed health economies, while halothane in many hospitals is no longer available. This is probably the reverse of the situation in developing health economies. Sevoflurane has less direct myocardial depressant effect than halothane and in normal children the concomitant fall in SVR and lack of change in heart rate resulted in no change in cardiac index [42]. Isoflurane preserves contractility, increases heart rate, and decreases SVR in children with CHD [43]. However, greater myocardial depression occurs in neonates [44]. Qp:Qs ratio was not changed from baseline in patients with ASD or ventricular septal defect (VSD) older than 6 months, with isoflurane, sevoflurane, or a fentanyl/midazolam anesthetic [45].

Intravenous agents such as propofol, midazolam, and ketamine are all used for sedation and general anesthesia. Propofol has been studied in children with CHD undergoing cardiac catheterization and has been shown to decrease SVR, resulting in significant changes in Qp:Qs calculations [46]. In patients with elevated PVR, propofol causes pulmonary vasodilation [47]. It also causes varying degrees of bradycardia [48]. Midazolam can be given orally, nasally, or intravenously. It has widespread use as an oral premedication in children, and the use of oral midazolam and ketamine has been adopted for cardiac catheterization. However, intravenous supplementation was required quite frequently and airway obstruction was also reported [49]. A bolus dose of midazolam given to children following repair of CHD caused hypotension and a fall in cardiac output [50]. Ketamine causes sympathetic stimulation, salivation, and vivid dreams or nightmares. It has negative inotropic effects on isolated myocardium, but this is masked in the intact patient due to the well-recognized sympathomimetic effects. Ketamine increases oxygen consumption (VO\(_2\)), which is a potential source of error in hemodynamic calculations, unless VO\(_2\) is actually measured [51]. Etomidate has been used for induction of anesthesia in children with CHD and end-stage cardiomyopathy, but there are few published data regarding its use during cardiac catheterization [52,53]. Dexmedetomidine is a newer sedative drug with centrally mediated, \(\alpha\)-agonist effects. It reduces sympathetic tone, increases parasympathetic tone, and causes sedation, anxiolysis, and mild analgesia with minor hemodynamic effects. This agent is not approved by the US Food and Drug Administration for use in infants and children. A single series report of its off-label use in cardiac catheterization concluded that it was not suitable as a single agent, despite the theoretical attractiveness of the pharmacodynamic profile [54]. There are editorial reviews both for and against its use in CHD [55,56]. There are some potentially troubling side-effects, including seizure, adverse effects on PVR, and hypertension. Two recent publications raise concerns about its use in patients with conduction defects: in a case report, a patient suffered intractable bradycardia and hypotension attributed to dexmedetomidine, and in the study by Hammer et al. the authors concluded that it should not be used for electrophysiological studies, and
that caution should be exercised in patients at risk from heart block or bradycardia [57,58].

The use of short-acting intravenous opioids such as alfentanil and remifentanil for sedation of spontaneously breathing children has also been reported [59,60]. These drugs are generally associated with good hemodynamic stability. The problems of respiratory depression and vomiting limit the usefulness of these agents unless the airway is controlled. The use of remifentanil with sevoflurane and positive pressure ventilation is associated with a decrease in heart rate and arterial blood pressure [61].

The patient with pulmonary hypertension

Primary pulmonary hypertension is rare in children as in adults. However, children with CHD and large left-to-right shunts are at risk of acquired pulmonary hypertension if their cardiac anomaly is not dealt with in a timely fashion. Infants with outflow obstruction to the pulmonary vascular bed, e.g., mitral stenosis or pulmonary vein obstruction, are also at risk.

When surgery is planned for children with shunts between the left and right circulation and pulmonary hypertension, it is important to carefully assess vascular reactivity, as this is crucial in deciding whether or not the lesion is operable. For children with pulmonary hypertension in the absence of such shunts, the question being asked is more likely to center around confirmation of diagnosis and response to specific therapeutic strategies. These investigations, more than any other, require teamwork on the part of the anesthesiologist and cardiologist. Children with severe pulmonary hypertension are at risk of sudden death and require careful anesthetic management [27,28]. Children whose pulmonary vascular bed is labile can appear inoperable if improperly managed.

Pulmonary hypertension ultimately results in right ventricular failure. The thin-walled right ventricle (RV) responds to pressure loading by dilating and becoming hypertrophied. This reduces right coronary blood flow rendering the subendocardial region vulnerable to ischemia. The dilated RV interferes with left ventricle (LV) geometry and function, causing increased left ventricular end-diastolic pressure and decreased stroke volume. Sudden increases in PVR may result in the interventricular septum bowing out into the left ventricular outflow tract, causing subaortic stenosis and further jeopardizing coronary perfusion. Tricuspid regurgitation can also occur. Acute changes in PAP and PVR are particularly poorly tolerated and cause reduction in cardiac output, arrhythmias, and death.

The intimate relationship between PVR, alveolar oxygenation, and carbon dioxide means that the first principle of anesthetic management of the child with pulmonary hypertension is meticulous attention to the airway and to gas exchange. Hypercarbia or hypoxia will cause an elevation in PVR. Details such as ineffective bag-and-mask ventilation, or too large a leak around the endotracheal tube, can result in life-threatening acute increases in PAP in vulnerable children. This is particularly important if there is no intracardiac shunt (e.g., patent foramen ovale, secundum ASD).

The rationale behind the management of children undergoing investigation of pulmonary hypertension is to establish the baseline hemodynamic values and then intervene to assess the reactivity of the pulmonary vascular bed. This also provides data against which the effects of therapy can be measured. Decisions are based on the lowest value of PVR that can be attained.

Use of endotracheal intubation and positive pressure ventilation allows for control of respiratory variables (such as arterial carbon dioxide, inspired oxygen) and reliable means to administer inhaled agents such as nitric oxide.

Premedication with oral midazolam is routine. Cautious inhalation induction with sevoflurane may be used if vascular access is difficult. This avoids the inevitable agitation due to multiple attempts at venipuncture. However, intravenous access is obtained at the earliest moment. The patient is ventilated with air and oxygen at an FiO2 as close to 21% as can be tolerated and the pH and PCO2 are maintained within normal limits, while intracardiac pressures and saturation are measured on both the left and right sides of the heart. Calculation of PVR will rely on measurement of PAP and estimation of PA flow (measurement of saturations and measurement or estimation of oxygen consumption allowing calculation of cardiac output and Qp:Qs). Measurements are usually repeated with a higher FiO2 and possibly hypocarbia produced by hyperventilation. Patients who do not respond to hyperoxia and hypocarbia are given inhaled nitric oxide (20–40 mmHg) and the study repeated. In selected patients, oral sildenafil or other treatments are started and the measurements are repeated some weeks later. The outcomes and complications of anesthesia and pulmonary hypertension in children were reported from a single center by Carmosino et al. [27]; the mortality is high, at 7–10% in patients whose PAP was higher than systemic blood pressure, regardless of anesthetic strategy. All the major complications occurred during cardiac catheterization. See Chapter 28 for an extensive discussion of pulmonary hypertension.

Endocardial biopsy

Endocardial biopsy is used in the routine surveillance of patients after cardiac transplant, in the assessment of patients with suspected rejection of the transplanted heart, and in the diagnosis of myocarditis and cardiomyopathy. The latter two groups are more likely to have myocardial dysfunction. When seen preoperatively, all patients should be questioned as to symptoms of heart failure or arrhythmia, and reports of preoperative echocardiograms and electrocardiograms (ECGs) inspected. The procedure is usually performed by cannulation of the right internal jugular vein. The biopsy catheter is passed into the heart and samples of endocardium are taken for histology. Stress testing, coronary angiogram, and ultrasound examination...
of the coronaries may be performed during the same procedure. There is a higher risk of perforation in dilated cardiomyopathy and in small infants due to the thin RV wall.

KEY POINTS: DIAGNOSTIC CATHETERIZATION

- All sedative, anesthetic, and analgesic agents have an effect on cardiac function and hemodynamics. Anesthesia must be planned to ensure the data collected truly reflect the patient’s physiology.
- Patients presenting are more frequently smaller and sicker, posing further challenges for the anesthesiologist.
- Patients presenting with pulmonary pressures higher than systemic pressures have a higher mortality regardless of anesthetic technique.

Interventional cardiology

As the number of diagnostic catheterizations has diminished, the use of cardiac catheterizations for therapeutic purposes has increased steadily [62,63]. Interventional procedures are done as an alternative to surgery and as an adjunct to surgical treatment. They are used in situations where surgical results are suboptimal, or to avoid the use and complications of CPB. During interventional catheterization, the focus is on treatment, not precise diagnosis, and maintenance of baseline hemodynamics is less critical. Some procedures are associated with marked hemodynamic disturbance and are performed in high-risk patients. The potential for serious complications is high. The need for mechanical support of the circulation is unusual but certainly not unheard of, and it is important to have systems and protocols in place for the instigation of mechanical support in the facility [64]. Children also undergo catheterization while on ECMO [65]. Individuals caring for patients need familiarity with the issues around the instigation and maintenance of mechanical support.

Anesthetic considerations

The types of patients presenting for interventional procedures range from those with asymptomatic disease presenting for day-case procedures to critically ill neonates undergoing procedures associated with marked hemodynamic disturbance (Table 29.3). The anesthetic approach should be tailored to the individual patient and it is important that the anesthesiologist appreciates the nature of the procedure to be performed. Sedation techniques may be appropriate on occasion; however, transcatheter interventions raise a number of specific concerns. The airway should be controlled during procedures associated with a high risk of hemodynamic instability, or of serious complications likely to require further interventions or resuscitation. Aortic valvotomy, dilatation of severe pulmonary stenosis, and closure of VSD should be considered absolute indications for general anesthesia and tracheal intubation. TEE is used during many procedures and necessitates tracheal intubation.

Patient movement or coughing during device or balloon placement may have disastrous consequences, and some interventions, e.g., pulmonary angioplasty, may induce coughing. A combination of sedation techniques with an additional bolus of an intravenous anesthetic, such as ketamine, to ensure stillness during interventions has been described [66]. It is not clear what advantage is offered by this technique over general anesthesia with control of the airway.

Interventional cardiology techniques

Valvuloplasty

The techniques used for balloon dilatation of stenotic aortic, pulmonary, mitral, or bioprosthetic valves are essentially similar. A catheter is introduced past the stenosis and pressures are measured proximal and distal to the stenosis. A wire is positioned across the valve and the catheter is withdrawn. The wire is used to guide a balloon catheter into position across the stenotic valve and to stabilize the balloon. The size of balloon used is selected relative to the valve annulus. The purpose of the procedure is not to dilate the valve annulus, but to separate the fused valve leaflets. Larger balloons improve the reduction in gradient but increase the risk of regurgitation. During inflation, the valve is completely obstructed and sustained single inflations are avoided. When a balloon is inflated across a stenotic valve, a “waist” is seen at the site of stenosis. Short inflations are repeated until this waist disappears [67].

Angioplasty

Vascular angioplasty involves the inflation of a balloon across an area of vascular stenosis. The technique is similar to balloon valvuloplasty and results in tearing of the endothelium and subsequent healing by scar formation and re-endothelialization. A modification of this technique is the use of cutting balloons, with small blades on the outside of the balloon, which are used for resistant stenoses. The technique may be applied to native blood vessels or to stenotic surgical conduits. Established indications are recurrent aortic coarctation, systemic venous stenosis, and PA stenosis. Complications include rupture of vessel, dissection, late aneurysm formation, thrombosis, and restenosis.

Endovascular stents

Modification of balloon angioplasty by the placement of endovascular stents has been applied to PA stenosis, systemic venous stenosis, and aortic coarctation [68]. The placement of endovascular stents improves initial success, reduces the incidence of recurrence, and may reduce late aneurysm formation. The stents used are deployed over a
### Table 29.3 Indications for transcatheter interventional procedures

<table>
<thead>
<tr>
<th>Class I: Generally agreed indication</th>
<th>Class II: May be indicated</th>
<th>Class III: Not indicated</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Balloon dilation of cardiac valves</strong></td>
<td>Pulmonary stenosis</td>
<td>Asymptomatic aortic stenosis (if wishes to become pregnant, strenuous activity)</td>
</tr>
<tr>
<td></td>
<td>Aortic stenosis with mean gradients &gt; 50 mmHg or symptomatic</td>
<td>Dysplastic pulmonary valve</td>
</tr>
<tr>
<td></td>
<td>Rheumatic mitral stenosis</td>
<td>Congenital mitral stenosis or restenosis</td>
</tr>
<tr>
<td></td>
<td>Pulmonary stenosis with complex heart disease</td>
<td>Pulmonary atresia without RV-dependent coronary circulation</td>
</tr>
<tr>
<td><strong>Balloon angioplasty</strong></td>
<td>Re-coarctation of aorta</td>
<td>Native coarctation of aorta</td>
</tr>
<tr>
<td></td>
<td>Systemic venous stenosis</td>
<td>Distal PA stenosis</td>
</tr>
<tr>
<td></td>
<td>Significant peripheral branch PA stenosis or in small patients where stenting is not an option</td>
<td>Large branch PA stenosis not amenable to stenting</td>
</tr>
<tr>
<td></td>
<td>Acquired pulmonary vein stenosis after RF ablation, lung transplant or compression due to tumors in older children</td>
<td>Main PA stenosis with pressures &gt; 2/3 systemic</td>
</tr>
<tr>
<td><strong>Stent placement</strong></td>
<td>Recurrent coarctation of aorta as long as sufficient size and safe for stent placement</td>
<td>Critically ill postoperative cardiac patient with branch PA stenosis causing compromise</td>
</tr>
<tr>
<td></td>
<td>Branch PA stenosis where can be expanded to adult size</td>
<td>Main PA stenosis with elevation of RV pressures</td>
</tr>
<tr>
<td></td>
<td>Acquired pulmonary vein stenosis after RF ablation, lung transplant, or compression due to tumors in older children</td>
<td>Palliation of severe branch PA stenosis</td>
</tr>
<tr>
<td></td>
<td>Baffle obstruction following atrial switch</td>
<td>Significant systemic venous obstruction inferior to clavicles and above inguinal ligaments</td>
</tr>
<tr>
<td></td>
<td>RV–main PA/PA conduit</td>
<td>Coarctation of aorta</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Isolated congenital pulmonary vein stenosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PDA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pulmonary vein stenosis after surgical repair for anomalous connections</td>
</tr>
</tbody>
</table>
### Atrial Septostomy
- TGA
- Decompression of left atrium

### Secundum ASD Closure Devices
- Hemodynamically significant secundum ASD

### Other Closure Devices
- Symptomatic PDA
- Symptomatic AP collaterals
- PFO
- Surgical shunts
- Pulmonary AV fistula
- Clinically veno-venous connections
- Symptomatic coronary AV fistula
- Symptomatic PVL (high risk for surgical intervention)

### Notes
- Patients who have experienced sequelae of paradoxical emboli
- R-L shunt and cyanotic (as long as not needed for maintain cardiac output)
- Risk of thromboembolic events
- “Silent” PDA
- Asymptomatic PDA with heart murmur
- AP collaterals in asymptomatic single-ventricle patients
- AP collaterals with pulmonary atresia with adequate dual supply from native pulmonary arteries
- Asymptomatic moderate to large coronary AV fistula
- MVSD
- Fenestrated Fontan
- Fontan baffle leak

### ASDs other than secundum variety
- PDA with irreversible pulmonary obstructive disease
- Inlet MVSD with inadequate space between defect and valves
- Small to moderate-sized MVSD without symptoms (expectation will become smaller over time)
- AP collaterals (without dual supply)
- AP collaterals in symptomatic single-ventricle patients
- Surgical shunts where cardiac defect is not corrected if develops hypoxemia with balloon occlusion of shunt

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RV, right ventricle; LV, left ventricle; PA, pulmonary artery; PDA, patent ductus arteriosus; TGA, transposition of the great arteries; HLHS, hypoplastic left heart syndrome; TAPVC, total anomalous pulmonary venous connection; LA, left atrium; ASD, atrial septal defect; PFO, patent foramen ovale; AP, aortopulmonary; MVSD, membranous ventricular septal defect; AV, arteriovenous; PVL, paravalvular leaks, IVS, intact ventricular septum.

Data from Feltes et al. [32].
balloon. When in position, the balloon is inflated to dilate the stent and the vessel. The balloon is then withdrawn, leaving the stent in situ.

Limitations of the technique are the large size of catheters required to deploy stents and that stents may narrow over time, due to endothelial proliferation. There are also absolute limits to the dilation of a stent. Large catheters increase the risk of damage to vascular and cardiac structures, especially thrombosis of the femoral vessels. Further complications are malposition or embolization of the stent. There are a myriad technical improvements under investigation, including drug-eluting stents, which are in commercial use, and bioabsorbable stents, which would “disappear” after a period of time.

**Closure of shunts**

A number of devices are available to close intravascular shunts. For smaller shunts, the most commonly deployed are helical wire coils available in different diameters and lengths. More complex devices are required for larger vessels and for closure of intracardiac connections. The most commonly used devices have a double umbrella design. They are deployed with the two sides of the “umbrella” on either side of the orifice. Complications are malposition or embolization of the device, vascular occlusion, myocardial perforation, hemolysis, and vascular trauma. The larger devices require large catheters to deploy them and may not be suitable for use in small infants.

**Treatment of specific lesions**

**Pulmonary valvuloplasty**

Percutaneous balloon pulmonary valvuloplasty has now been performed for over 30 years. It is indicated when the mean transvalvular gradient is greater than 40 mmHg with a normal cardiac output, and is the treatment of choice for isolated pulmonary valve stenosis. It is also useful therapy in selected patients with pulmonary atresia, and tetralogy of Fallot. Immediate results are excellent with most patients with isolated pulmonary stenosis, not requiring further intervention for 10 years.

Neonates with critical pulmonary stenosis can be critically ill and cyanosed. The pulmonary circulation is dependent on flow from the ductus arteriosus (PDA), as there is minimal flow through the pulmonary valve. Many infants will be mechanically ventilated because of profound hypoxia and the use of prostaglandin (PGE$_1$) infusion to maintain ductal patency. The open ductus and minimal flow through the pulmonary valve means that inflation of the balloon often does not cause further hemodynamic compromise. Acute complications in 10–30% of patients have been reported [69,70]. The RV is pressure overloaded by the pulmonary stenosis and will not immediately recover, even after complete relief of the outflow obstruction. Continuation of PGE$_1$ infusion maintains pulmonary flow during this period. The size of the valve annulus, tricuspid valve size, and ventricular volume are predictors of outcome [71].

In older infants, in whom the PDA is closed, inflation of the balloon leads to complete obstruction of the RVOT and greater hemodynamic upset. Cardiac output decreases dramatically, resulting in significant hypotension. This usually improves on deflation of the balloon, but if ventricular dilatation has occurred, this may not be the case. Bolus epinephrine and occasionally more prolonged inotropic support may be required.

A modification of the technique is used for treatment of pulmonary atresia with intact ventricular septum.
(Figure 29.3). Patients present in a similar way to neonates with critical pulmonary stenosis. Radiofrequency or laser energy is used to perforate the membrane. More recently, stenting of the PDA has been used in conjunction with radiofrequency (RF) valve perforation, which has led to a significantly lower early reintervention rate than valve perforation alone [72]. One comparative study of surgical valvotomy vs. RF valvotomy demonstrated that mortality was lower in the RF group; however, the increased mortality in the surgical group may be explained by the greater complexity of patients in this group [73].

**Pulmonary arterial angioplasty**

Pulmonary artery stenosis may be congenital or acquired, often following surgery. Congenital stenosis is seen in association with other abnormalities with reduced pulmonary blood flow (such as tetralogy of Fallot), as branch stenosis in association with Williams syndrome or congenital rubella, or as an isolated stenosis at the site of insertion of the PDA. Stenosis may occur after any surgery involving manipulation of pulmonary arteries, particularly shunt formation or PA banding. The site of stenosis may be any point in the pulmonary vascular bed, and multiple sites are not uncommon (often associated with a poorly developed pulmonary vascular bed and collateral vessels). Two-thirds of stenoses are confined to proximal vessels.

Surgery may be used for proximal PA stenosis, but surgical treatment of peripheral PA stenosis is difficult. Angioplasty is initially successful in 50%, but restenosis is common and long-term benefits are seen in less than 35% of patients [74,75]. In a report of 1,315 pulmonary angioplasty and/or stent placements, severe procedural adverse events occurred in 10% of patients [76] and two patients died. Complications included trauma to the heart or vessels, malposition of the stent, balloon rupture and arrhythmia. Pulmonary edema and hemoptysis were thought to be due to reperfusion injury and occurred in 40 patients. Events purely related to anesthesia or sedation occurred in 12 patients. The use of cutting balloons increased the effectiveness of treatment [77–80] but was associated with increased incidence of adverse events.

The use of endovascular stents reduces the incidence of initial failure and restenosis (Figure 29.4). A single-center report of long-term follow up of stenting demonstrated good outcome [81]. There are limited data available on the long-term outcomes of endovascular stents in infants, but it is a safe technique with good intermediate outcomes [82]. When positioned in a stenotic PA, the large catheter may increase the degree of obstruction, resulting in worsening hypoxia and right ventricular failure. Children with RV hypertrophy from peripheral pulmonary stenosis may also deteriorate hemodynamically as a result of tricuspid regurgitation from the catheter.

Patients in whom pulmonary blood flow is dependent on cavopulmonary shunts have a limited capacity to tolerate any obstruction to pulmonary blood flow. Obstruction can occur at the site of the venous to PA anastomosis, at the site of previous surgery, or at a remote site. Angioplasty, commonly with placement of stents, may be used to relieve the obstruction. When required in the early postoperative period, the patient’s condition is often poor.

Patients with Williams syndrome often have multiple peripheral stenoses of the pulmonary arteries and associated supravalvular aortic stenosis, carotid, renal artery and coronary artery stenosis. In a series of 39 procedures, the mortality rate was 7.7% [83]. High right ventricular pressure was a predictor of mortality and the creation of an ASD in these patients may have been beneficial. Out of 22 patients initially managed with deep sedation without endotracheal intubation, three required intubation.

**Percutaneous pulmonary valve implantation**

Percutaneous pulmonary valve implantation is now established practice, with the first report in 2000 [84].
This procedure is performed in patients with previous RVOT surgery, most commonly (95%) in patients with an RV–PA conduit that has either become stenotic or has significant pulmonary regurgitation, or both. Tetralogy of Fallot (60%), previous Ross procedure (10%), and truncus arteriosus (10%) are the predominant diagnoses [85]. Inclusion criteria are that the patient must meet surgical criteria for valve placement, including RV pressure two-thirds to three-quarters of systemic, or severe pulmonary insufficiency, and outflow tract dimensions 14–22 mm in two dimensions. In addition, the patient’s weight needs to be greater than 20 kg and the median patient age is 18–22 years for this procedure. Under general endotracheal anesthesia, a 21 Fr sheath is used to access a femoral vein, and the valve mounted inside a balloon-expandable stent is cramped inside the sheath, and threaded along a guidewire to the correct position under conventional biplane fluoroscopic guidance. The valve is then re-expanded to its final diameter with enough force to prevent migration or paravalvular leak [86] (Figure 29.5).

A case series in 2008 reported that six out of 152 patients (3.9%) required emergency surgery, including homograft rupture in two patients, dislodged stented valve in two patients, occlusion of right PA in one patient, and occlusion of left main coronary artery in one patient. All six patients survived but one had neurological sequelae from prolonged resuscitation after homograft rupture [87]. Significant hemodynamic instability and blood loss will occur in some patients, and surgical and operating room backup plans should be in place for these procedures. Immediate hemodynamic results are favorable, with a significant reduction in RV pressure and relief of severe pulmonary insufficiency, and long-term freedom from reoperation is 84% up to 50 months after the procedure.

**RVOT stenting**

Classically, treatment of a narrowed RVOT with reduced pulmonary blood flow has been surgical. Creation of a systemic-to-pulmonary artery shunt remains high risk in a variety of patients, such as those with low weight or other complex cardiac lesions. Stenting of the RVOT can be an alternative and case reports have shown favorable outcomes [88–91]. The largest case series is from Birmingham Children’s Hospital, UK, involving 52 patients [88]. They describe techniques of both native pulmonary valve preservation (with balloon valvuloplasty being performed at the same time) and stenting across the valve. In those with hypoplastic pulmonary arteries, pulmonary tree growth is promoted. Complications of the procedure include perforation of the RVOT. The Birmingham group had no incidences of ventricular arrhythmias, atrioventricular (AV) block or myocardial ischemia.

**Aortic valvuloplasty**

Balloon dilatation of isolated aortic valve stenosis is indicated when the mean transvalvular gradient is greater than 50 mmHg or is greater than 40 mmHg with symptoms, or when ECG evidence of ischemia is seen. Neonates may have much smaller gradients despite severe stenosis, as flow across the aortic valve will be minimal, the systemic circulation being supported by right-to-left flow through the PDA. Untreated severe stenosis carries a 19% risk of sudden death [67,92]. In a series of 630 dilatations, the immediate outcome was suboptimal (failure or major

![Figure 29.5](image-url)
morbidity) for 17% of patients and procedural mortality was 1.9% [93]. Major complications, including aortic regurgitation, vascular damage, and perforation of heart or great vessels, occurred in 6.3% of patients. Age < 3 months, high gradient prior to the procedure, the use of small balloon sizes, and the presence of an aortic coarctation predicted poor outcome. UK figures for 2009–2012 demonstrate similar 30-day mortality, with half of deaths occurring in neonates [31] though 1 year mortality rose to 5%. The procedure is essentially palliative. However, in a single-center study with up to 17 years of follow-up, two-thirds of patients had a decade of freedom from surgical intervention [94]. The valve may be damaged by use of an oversized balloon causing dilation of the valve annulus, or by inadvertent puncture of the valve leaflet. The latter complication may be reduced by use of an antegrade approach to the valve via the atrial septum (puncturing the septum if the foramen ovale is closed). This approach reduces the risk of damage to the femoral artery, passage of the wire across the stenotic valve is simplified, and less hemodynamic compromise occurs. Should severe aortic insufficiency occur, coronary blood supply is compromised and urgent surgical repair may be required. The mortality in this situation is high [95].

Neonates present significant challenges, for both immediate and long-term management. The decision-making can be complex [96] and there is often considerable hemodynamic instability and risk of sudden death from myocardial ischemia and arrhythmia. The systemic and coronary circulations are dependent on right ventricular flow through the PDA and the LV is greatly hypertrophied with poor compliance. Initial resuscitation includes mechanical ventilation, PGE₁, and cautious use of inotropes. Inflation of the balloon across the aortic valve will lead to transient complete obstruction of coronary flow. An opioid-based anesthetic technique reduces cardiac work and minimizes afterload reduction and tachycardia. Care must be taken to maintain preload, as any reduction in diastolic blood pressure can lead to further ischemia. Inotropes, vasopressors, and a defibrillator should be immediately on hand. A more recent study described 13% early mortality, with the presence of endocardial fibroelastosis as a significant risk factor [97]. Older infants may present with severe degrees of aortic stenosis [98]. They have heart failure and are at risk of ischemia and arrhythmia. Cardiovascular compromise during balloon inflation is inevitable, but on deflation of the balloon, prompt return of cardiac output is to be expected. The incidence of arrhythmia is higher than during other interventional procedures. The use of rapid ventricular pacing to decrease cardiac output can be helpful and is associated with good technical conditions and stable hemodynamics [99]. As with neonates, there is a risk of arterial damage and of aortic regurgitation. The latter may require surgical intervention. The need for the patient to be still during positioning of the balloon and the risk of hemodynamic compromise or complications must be considered. Older patients may present with progressive aortic stenosis or restenosis.

Coarctation of aorta

Angioplasty is applied to both native and recurrent coarctation of the aorta [100–102]. The indications are resting hypertension proximal to the coarctation with a mean gradient of >20 mmHg, or presence of multiple collaterals. The best results are obtained when there is a short discrete coarctation with an otherwise normal aortic arch. Initial success with native coarctation is greater than...
for recurrent coarctation; however, there is a high incidence of late aneurysm formation (2–6%) and of restenosis (7–12%). In neonates, re-coarctation rates are high and surgery is the preferred treatment, except in neonates with severely depressed cardiac function or severe co-morbidities. In older children with native coarctation, the role of angioplasty is controversial, although catheter interventions are often considered after 4–6 months of age [29,32]. Surgery for recurrent coarctation is more difficult and re-coarctation is an accepted indication for angioplasty. Use of endovascular stents may reduce both restenosis and aneurysm formation, but the risk of damage to the femoral artery and the failure of stents to grow with the patient limit the use of this technique. The anesthesiologist can be thankful that the controversy centers around medium- and long-term outcomes. In the majority of cases, perioperative complication is unusual, especially with the use of covered stents. No procedural-related death was reported in the UK from 2009 to 2012. Adult patients may present with re-coarctation or with aneurysm formation.

**Closure of ASD and VSD**

Selected ASDs are suitable for device closure; ideally secundum ASDs with a rim of tissue on all sides and separation from valves and the venae cavae. The technique is unsuitable for ostium primum defects or for large defects. Newer devices and modification of techniques may allow closure of defects with less developed rims on at least one side.

Complications are uncommon but include embolization of the device, encroachment on AV valves, obstruction of pulmonary or systemic veins, perforation of the heart or great vessels, and air emboli. Generally the procedure is well tolerated. It is usually performed under general endotracheal anesthesia due to the use of TEE (Figure 29.6) and the need for a still patient. The use of TEE to aid placement of ASD devices is discussed in Chapter 12. Endovascular and transthoracic echocardiography guidance may also be employed. ASD devices are also used to close Fontan fenestrations, if spontaneous closure has not occurred.

Transcatheter closure of a VSD is a more complex procedure, with greater risk of serious complications [103]. Relatively few congenital VSDs are suitable for device closure. Complications include blood loss, arrhythmia, AV or aortic valve regurgitation, and cardiac arrest [104]. General anesthesia and control of the airway are required due to the high risk of cardiovascular instability, the length of the procedures, and the use of TEE. The likelihood of complications, and hemodynamic instability during the procedure depend in part on the patient population. The elective closure of a congenital defect is much more straightforward than the management of an adult with an acute VSD as a result of a septal wall infarct.

**Closure of extracardiac connections**

Connections between the systemic and pulmonary circulations may occur in isolation (PDA), in association with CHD (aortopulmonary connections with pulmonary atresia), as a result of palliation of cyanotic heart disease (venovenous connection after cavopulmonary connection), or as surgically created shunts [105].

Often, naturally occurring lesions are closed by embolization with helical wires. Choice of anesthetic technique will depend on the patient’s physiology. Cyanosed patients with a cavopulmonary connection and multiple collaterals may respond poorly to positive pressure ventilation. Older patients presenting with large PDAs may have significant pulmonary hypertension and be at risk of right heart failure.

**Atrial septostomy**

Balloon atrial septostomy was first described in 1966 [106]. The objective is to open an unrestrictive connection.
between left and right atria, to allow bi-directional mixing of blood. It has been most widely used for the initial palliation of transposition of the great arteries and, in this situation, the improvement in the patient’s condition may be dramatic. Further indications are total anomalous pulmonary venous drainage, AV valve atresia, and pulmonary atresia with intact ventricular septum.

The technique involves the passage of a balloon-tipped catheter across the foramen ovale into the left atrium. The balloon is inflated and withdrawn (often with some force) across the septum, tearing the atrial septum. This procedure is repeated until the inflated balloon can be withdrawn without resistance. The procedure can be performed at the patient’s bedside using echocardiographic guidance. A modification of the procedure is applied to older infants. At 1 month of age, the atrial septum is too thick to be torn by the balloon alone. A catheter with a retractable blade is used to initiate the tear. Indications are similar to balloon atrial septostomy.

Complications include arrhythmia, perforation of the heart, tricuspid regurgitation, balloon rupture, and embolization and damage to heart structures. Patients are frequently in a very poor condition. They are often extremely hypoxic, acidic, and may have pulmonary edema. They will generally require ventilation and PGE\textsubscript{1} infusion. Attempts to improve the patient’s condition, beyond basic resuscitation, are more often than not futile, and should not lead to delay in conducting the procedure. There is significant risk of life-threatening arrhythmia due to catheter manipulation in an irritable myocardium.

Patients with HLHS and a highly restrictive atrial septum represent a very high-risk population. The pulmonary venous return is in effect obstructed and the child will be severely hypoxic and in a poor condition. Atrial septostomy will result in a sudden increase in pulmonary blood flow, which may improve arterial saturations, but can also result in marked hemodynamic compromise. Early palliation with surgery or a hybrid procedure (which will include atrial septostomy) is likely to be a better option if aggressive treatment is to be continued. Long-term outcome in this group is also poor.

**Ductus arteriosus stenting**

Initial results of stenting the ductus arteriosus, to establish a reliable source of pulmonary blood flow, were discouraging. Recently, with improvements in coronary stents and their delivery systems, the outcome from the procedure has become more favorable. Stenting the ductus arteriosus can avoid complications associated with surgical placement of an aortopulmonary shunt. The procedure is not, however, without short- and longer-term problems and these patients can often be challenging to manage.

Restenosis of the stent is common and may require repeat dilation. Stenting should only be performed on patients who require palliation for no longer than 3–6 months. [32] Residual stenosis, or restenosis, can be reduced by placing the stent along the entire length of the ductus and use of long-term antiplatelet therapy post-procedure.

It is usual to stop or reduce prostaglandin infusions prior to the procedure. This is to produce a reduction in the duct diameter, allowing the stent to be anchored, and reducing the risk of embolization [107]. The patient’s arterial saturations will decrease during this period and the patient should be carefully observed; if necessary, the prostaglandin should be restarted. In stenotic or tortuous ducts, Schranz et al. only stopped the infusion after successful stent placement [108]. Some authorities require that the PDA not be the sole source of pulmonary blood flow; e.g., there should be some existing flow through the pulmonary valve, or pulmonary atresia with thin valve leaflets that can be perforated and dilated before ductal stenting.

On occasion, the ductus will respond to instrumentation by developing spasm. This will cause increasing hypoxemia which may be life-threatening. Efforts should be made to increase systemic arterial pressure, and the prostaglandin infusion should be restarted after consulta-
tion with the cardiologist. A bolus dose of prostaglandin may also be considered; however, if hypoxemia is refractory and life-threatening, then mechanical support of the circulation (with bypass or ECMO) may be required. Attempts to continue with the procedure may subsequently be made, but surgical shunt is likely to be a more reliable option in this situation. Other complications include malposition or embolization of the stent, which may prove difficult to retrieve and may impinge upon pulmonary or systemic blood flow. As with surgical shunts, there exists, following the procedure, a balance between systemic and pulmonary blood flow. It is necessary to be alert to both excessive and inadequate pulmonary flow during this period.

Selection criteria for this procedure will preclude many patients, who will then require a surgical shunt. Those with a more tortuous ductus present technical challenges and stenting may not be successful [109]. However, there have been reports where tortuosity of the duct did not prevent stent implantation [108,110,111]. Other exclusion criteria include pre-existing branch PA stenosis [109] and weight < 2.5 kg [107]. Despite careful selection, there will be occasions when it will only become apparent during the procedure that stenting is not possible. The patient’s condition is likely to deteriorate during long procedures and accepting the need for a surgical shunt early, when faced with a technically difficult case, may often be wiser.

**Hybrid procedures**

This term refers to treatment of congenital cardiac defects using a combination of surgical and transcatheter interventions as part of a single procedure. It often refers to the treatment of HLHS but also includes periventricular closure of VSDs and branch PA stent placement among others. The discussion below will review hybrid palliation of HLHS.
The objective of hybrid palliation of HLHS is to allow the patient to survive and for the pulmonary circulation to mature, up to a point when a superior cavopulmonary connection is possible. Much of the surgical repair, integral to a first stage Norwood procedure (such as aortic reconstruction), will then be conducted at the time of this second procedure. Surgery during the neonatal period is not avoided, but CPB and aortic cross-clamping is avoided. It is hoped that this approach will reduce both short-term adverse consequences of bypass (myocardial dysfunction, inflammatory and stress responses, bleeding and transfusion) and long-term consequences, principally neurological injury. There is some evidence for the former contention. As yet, the latter is unproven. There is no clear survival advantage at this time [112–115], however the length of stay in the intensive care unit (ICU) appears to be reduced.

Indications for the choice of a hybrid procedure rather than conventional surgical palliation will vary between centers. In some centers, it is offered as a viable alternative to all patients, or is the preferred strategy. In others, it is restricted to patients perceived to be at higher risk for surgical palliation, i.e., weight < 2.5 kg or patients with unfavorable anatomy. With time, and greater experience of this procedure, the indications should become clearer.

This is a surgical procedure consisting of a median sternotomy, bilateral PA bands, and stenting of the PDA, which is done via a sheath placed either through the RVOT from the right atrium or directly into the main PA (Figure 29.7). The sheath is secured with a purse string suture controlled by the surgeons, and the coronary stent (or two) is then deployed by the cardiologist. Angiographic control is required and will require adaption of the surgical space. There are opportunities for rapid blood loss, there can be obstruction of retrograde aortic flow and thus coronary and cerebral ischemia, and a significant incidence of atrial tachycardia has been described. Late stent occlusion and migration also occur, contributing to interval mortality. To prevent occlusion of retrograde flow (and death due to coronary insufficiency), shunts may be placed from the main PA to the innominate artery in patients with aortic atresia [114–116]. Indications for such shunts are just one of many controversies regarding this procedure.

Despite the intuitive appeal of avoiding CPB and a lengthy procedure, these patients often demonstrate a hemodynamic profile that is actually worse than standard operative therapy over the first 36–48 hours. In a comparison study of six hybrid vs. 13 standard Norwood stage I patients, the hybrid patients had higher Qp:Qs, lower mean arterial pressure, lower cardiac index, and higher serum lactates than standard stage I palliation [115]. These patients often need inotropic support, and careful ventilatory management and monitoring to balance Qp:Qs during, and after, the hybrid procedure, just as in the standard surgical approach. However, they improve more quickly than babies who have undergone CPB.

Galantowicz et al. [113] have reported intermediate term outcomes comparable to conventional staged surgical palliation for HLHS. Of 40 patients undergoing hybrid stage I, 36 survived for the comprehensive stage II procedure, 52% were extubated in the operating room, and 85% within 24 hours. Of these 36 patients, 33 (92%) survived stage II, and 15 patients have undergone stage III repair (Fontan completion) with no mortality. Overall interstage mortality was 5%, and catheter or surgical reintervention rate was

![Figure 29.7](image-url)
36%. ICU and hospital length of stay, and hospital charges compare favorably to standard approaches. Thus, the proof of concept for the hybrid approach to HLHS seems valid, and it is likely that this approach may be applied to other scenarios.

Most infants with HLHS have some restriction to flow through the atrial septum. As described earlier, pulmonary blood flow after hybrid palliation is often excessive, and atrial septostomy is likely to lead to a further increase. Septostomy is commonly not performed at the same time as PDA stenting and PA banding, unless the septum is highly restrictive. The optimal timing of septostomy is controversial. The Hospital for Sick Children, Toronto, has advocated delayed septostomy only if there is evidence on echocardiography of a gradient across the septum and the infant’s arterial saturation is less than 70%. Other units have proposed septostomy in all patients prior to discharge. Close attention needs to be paid during and immediately after balloon septostomy, because of the potential for poorly tolerated atrial arrhythmias, and also the development of pulmonary edema, systemic hypotension, and myocardial ischemia.

**Key Points: Interventional Cardiology**

- The anesthesiologist needs to have an understanding of the procedure performed and its complications to anticipate potential adverse events.
- Interventional procedures should not be performed (with the possible exception of balloon atrial septostomy) unless facilities and expertise for surgical exploration and mechanical support of the circulation with CPB or ECMO exist in the center.
- Aortic valvotomy, dilatation of severe pulmonary stenosis, and closure of VSD should be considered absolute indications for general anesthesia and tracheal intubation.
- The scope of “hybrid” procedures is expanding and should be performed under operating room standards.
- Patients undergoing a hybrid procedure may have a stormier period postoperatively than if undergoing a traditional surgical technique.

**Electrophysiology procedures**

Electrophysiology procedures include electrophysiological (EP) studies performed for treatment of tachyarrhythmias and implantation of pacemakers. The purpose of an EP study is to identify the mechanism of the patient’s arrhythmia by recording signals from electrodes placed within the heart. Use of fluoroscopy and reference to anatomic landmark allows localization of the abnormal pathways or foci responsible for the arrhythmia. Ablation of the abnormal pathway is initially successful in 91% of patients with a recurrence rate of 23% [117,118].

The majority of children presenting for EP investigation and treatment are otherwise healthy, have functionally normal hearts, and present with well-tolerated SVT. A minority will have either life-threatening arrhythmia or arrhythmia complicating CHD (7.9%) or cardiomyopathy (2.4%) [119]. Anesthetic concerns include the length of the procedure, poor access to the patient, the possibility of anesthetic agents altering the EP of the heart, and occasionally poor cardiac function. Chapter 18 presents an extensive discussion of arrhythmias.

**Pathogenesis of arrhythmia**

The most common mechanism of tachycardia is re-entry. This requires a circuit composed of pathways with different conduction velocities and refractory periods (see Figure 29.8). Pre-excitation syndromes are a subgroup of re-entry tachycardia, in which one arm of the circuit is the AV node and the other is a congenital muscular pathway between the atrium and the ventricle. The arrhythmia arises when depolarization occurs in the circuit while one limb is refractory and the other is able to conduct. The depolarization continues around the circuit and reaches the previously refractory pathway, which is now able to conduct [120]. Tachycardia will only perpetuate when the conduction velocity is slow enough or the circuit long enough so that the “head” of the arrhythmia circuit does not meet the “tail.”

Atrioventricular nodal re-entry tachycardia (AVNRT) is the most common cause of SVT, and is the diagnosis in approximately half of all ablations at our center (Alder Hey Children’s Hospital, UK). The normal AV node receives an input from two physiologically distinct pathways: a slow pathway conducting slowly with a short refractory period and a fast pathway that conducts quickly with a longer refractory period. Normal conduction occurs via the fast pathway. If an ectopic beat reaches the pathways while the fast pathway is refractory, the impulse is conducted via the slow pathway only. In some individuals, the conduction speeds and refractory periods of the two pathways are such that tachycardia is perpetuated due to a circuit comprising anterograde conduction via the slow pathway, retrograde conduction via the fast pathway, and conduction through the atrial myocardium.

A further mechanism is enhanced automaticity. During normal sinus rhythm, only cells in the sinoatrial (SA) node independently generate rhythmic impulses through spontaneous depolarization of the basement membrane. Other cells demonstrate this activity but at a slower rate and will only control the heart rate if the sinus node is not functioning or conduction is blocked. When cells are damaged and subjected to extrinsic factors (electrolyte disturbance, hypoxia, hypercarbia, high wall tension, ischemia, and high catecholamine levels), spontaneous depolarization may be accelerated. This leads to rapid repetitive depolarization of a single focus, referred to as ectopic or automatic tachycardia.
Figure 29.8 Re-entry tachycardia requires a circuit with two limbs of different conduction velocities and refractory periods. The left-hand limb of the circuit in the figures has a shorter refractory period and slower conduction velocity (curved arrows). In (A) neither pathway is refractory, and the impulse is conducted over both limbs. In (B) a premature impulse travels over the left-hand pathway; however, the right-hand pathway is refractory from previous conduction. If the right-hand pathway is no longer refractory by the time the impulse reaches the distal end of the circuit, it is conducted in a retrograde fashion via the right-hand pathway and the re-entry rhythm is perpetuated (C).

Ventricular tachycardia (VT) comprises less than 5% of ablation procedures conducted at Alder Hey. In patients with structurally normal hearts, the most common types are fascicular tachycardia and automatic tachycardia originating in the outflow of the RV. Fascicular VT occurs due a re-entry circuit involving the left bundle branch. In patients with operated CHD, VT may occur due to re-entry around scars tissue. This is more commonly seen in adults than in pediatric patients.

Electrophysiology techniques
Figure 29.9 demonstrates typical electrode catheter position during an EP study for investigation of SVT. The catheters have multiple electrodes along their length. An electrode placed across the tricuspid valve can be positioned to record an ECG from the bundle of His. Further electrodes are typically placed high within the right atrium, at the apex of the RV, and “roaming” electrodes can be placed elsewhere in the right heart. Potentials from the left heart can be recorded via an electrode within the coronary sinus or from electrodes placed directly within the left heart (via puncture of the atrial septum or retrograde passage through the aortic valve).

Figures 29.10 and 29.11 demonstrate typical EKGs recorded during an EP study. In order to identify the mechanism of the arrhythmia, periods of pacing and programmed stimulation are undertaken. Pacing, commonly via the coronary sinus, allows arrhythmia to be provoked.

Figure 29.9 Typical catheter position during an electrophysiological study for investigation of supraventricular tachycardia. Catheters have multiple electrodes along their length. Catheters are positioned across the tricuspid valve to record signal from the His bundle (H), in the right ventricular apex (V), in the high right atrium (A), and within the coronary sinus (CS). In this image, contrast has been injected into the coronary sinus. The coronary sinus electrode has been introduced via the left subclavian vein; however, it is also often introduced via the femoral vessels.
Simultaneous surface and intracardiac electrocardiograms (ECGs) are shown. Signals from the surface ECG are shown in blue, those from the electrode placed across the tricuspid valve (along the His bundle) are in red, and those from the electrode in the coronary sinus are in green. Annotations are shown in yellow. Three paced beats (P) are delivered at 600 ms intervals via the distal coronary sinus electrode (CS d) followed by a premature stimulus (E) resulting in supraventricular tachycardia. The atrial signal (with superimposed pacing spike) is labelled “A” and the ventricular signal “V.” During pacing the accessory pathway is refractory and conduction occurs via the atrioventricular (AV) node and bundle of His, indicated by a normal PR interval on the surface ECG and earliest repolarization in the His bundle electrode. After initiation of tachycardia, ventricular activation continues to be via the AV node; however, retrograde activation of the atrium occurs via the abnormal pathway, producing a re-entry tachycardia. Atrial activation during tachycardia occurs earliest in the distal coronary sinus electrode, indicating a left-sided pathway. (Source: Dr Mark Hall. Reproduced with permission.)

Radiofrequency ablation and cryoablation
Destruction of an abnormal pathway, the slow pathway of an AVNRT, or an automatic foci abolishes the arrhythmia. This is most often accomplished by delivering RF energy to heat and ablate the area. An alternative to RF ablation is cryoablation, the freezing of the foci. This allows for the pathway or foci to be temporarily disabled prior to its destruction. This can be a safer option when the pathway is close to the AV node, such as in AVNRT. In the treatment of pre-excitation syndromes, a specialized catheter is positioned along the AV ring, then adjusted to record the earliest conduction via the abnormal pathway. When delivering RF energy, the size of lesion created is dictated by the power. Temperature control is used to stop overheating of local tissue and blood. A further EP study is conducted following attempted ablation to test for residual or additional pathways. Mapping systems have been developed which allow the detailed anatomical mapping of heart structures, while limiting the use of fluoroscopy [121] (Figure 29.12). This can be especially valuable for mapping and guiding of ablation of ectopic foci within the atrium and structures such as pulmonary veins (which may commonly be the site of abnormal foci).

Arrhythmia in patients younger than 4 years may resolve spontaneously and indications are thus limited to life-threatening arrhythmia not controlled by anti-arrhythmic drugs. There have been recent reports of successful ablation in children younger than 2 years, but complications are more common [122, 123]. Such patients will frequently have abnormal ventricular function and
severe refractory arrhythmia prior to an EP study being contemplated. Arrhythmias in older children are less likely to resolve and the indications for ablation are wider. Indications include failure of medical treatment, risk of sudden death, and a patient’s preference for ablation rather than long-term treatment with anti-arrhythmic drugs. Patients are usually healthy, with well-tolerated intermittent arrhythmia.

**Arrhythmia in patients with CHD**

Patients with CHD may develop arrhythmia in a number of circumstances [124,125]. Ebstein’s anomaly is associated with accessory pathways and pre-excitation. Atrial dilation and scarring within the heart may complicate surgical palliation or repair of a CHD and is often associated with arrhythmia. The latter is especially true following extensive atrial surgery, such as Mustard procedure or classical Fontan connections. These patients may have poor reserve to tolerate tachycardia, and placement of intracardiac electrodes may be complex. In a series of 139 patients, RF ablation was possible in 66% of studies with a recurrence of 11% at 2 years. No significant morbidity was caused by the procedure [124]. A review article by Szili-Torok et al. outlines etiology, mechanisms, and possible new techniques for transcatheter ablation in CHD [126].

**Anesthetic considerations**

As with other catheter procedures, it is possible to conduct EP studies in conscious patients or with minimal sedation. However the procedures are often prolonged, multiple venous and arterial access points may be required, and periods of arrhythmia are inevitable, which may be unpleasant for the patient. Vascular access in the jugular or subclavian veins may be particularly intimidating for an awake patient. Deep sedation is unlikely to offer any advantage to anesthesia and the additive effect of repeated doses of sedative drugs over a period of time must be considered. In adults with atrial fibrillation, EP studies...
and ablation under general anesthesia have been shown to be more successful [127].

When seen preoperatively the patient should be questioned as to the frequency of arrhythmia, precipitating factors, their symptoms during the arrhythmia, and whether treatment is required for termination. Arrhythmias associated with fainting or collapse are likely to be associated with greater hemodynamic compromise. Anti-arrhythmic drugs are usually stopped prior to the procedure unless the arrhythmia is frequent and poorly tolerated. Other considerations include the presence of CHD, cardiomyopathy, or familial conditions associated with arrhythmia (long QT syndrome and arrhythmogenic right ventricular dysplasia). The majority of patients will be adolescents and it is important to be aware of privacy issues, autonomy, and risk-taking behavior. Pregnancy testing preoperatively is routine in many institutions, and is particularly important in view of the radiation exposure.

In most cases, the electrophysiologist is aware of the likely mechanism of arrhythmia from surface ECG or from Holter recording of the arrhythmia. This allows the anesthetic technique to be adapted to reduce the risk of suppression of the arrhythmia and to have minimal effects on the patient’s EP. Specific agents may suppress abnormal pathways or foci to a point where their detection and induction of the arrhythmia is not possible. This leads to false-negative studies and failure of the procedure.

Other considerations are the length of the procedures, poor access to the patient, and the potential for hemodynamic compromise. EP studies are often scheduled for 4 hours and can take longer. X-ray tables are very firm and patient positioning can be awkward. Care needs to be taken to avoid injury to nerves and pressure areas. Large adolescent patients may be particularly difficult to position. The need for vascular sheaths in the upper body can make positioning even more awkward and reduce access to the patient during the procedure.

Periods of tachycardia are to be expected during an EP study and healthy patients tolerate this well. Significant hemodynamic compromise occurs with very high ventricular rates or when the patient has a reduced cardiac reserve. Vasopressors may be used to improve perfusion pressure but α-adrenergic agonists have reflex effects on the EP of the heart. Discussion with the cardiologist prior to and during the procedure is vital in the management of more difficult patients. Most arrhythmias can be terminated rapidly by overdrive pacing. Drugs (other than
Anesthetic drugs and the cardiac conduction system

Anesthetic agents influence the EP of the heart. Effects are mediated via the sympathetic and parasympathetic systems or via direct effects on the cardiac conduction systems and myocardium. The significance of these effects depends on the mechanism of the tachycardia. Anesthetic drugs also slow cardiac conduction and can be associated with significant bradycardia, which may be due to vagal stimulation (fentanyl, remifentanil) or α-adrenergic blockade (clonidine). It has been stated that dexmedetomidine is contraindicated in electrophysiological studies or in situations where cardiac output is profoundly dependent on sympathetic tone [57,58]. Dexmedetomidine often causes bradycardia and will depress sinus node function and automaticity, and increase both PR interval and AV nodal block cycle lengths. See Chapter 6 for a further discussion of dexmedetomidine’s effects on cardiac conduction.

Anesthetic drugs and re-entry tachycardia

Supraventricular tachycardia due to re-entry requires conduction of impulses in a circuit, commonly involving either a functional AV node and accessory pathway (pre-excitation syndromes) or two inputs in or near to the AV node (AVNRT). In pre-excitation syndromes, the effect of anesthesia can be characterized by two EP variables: the accessory pathway effective refractory period (APERP) and the critical coupling interval [128]. The APERP is the minimal time between two impulses that are still conducted by the accessory pathway. The critical coupling interval is the maximal time between two impulses that will precipitate an SVT. In AVNRT, anesthetic agents will commonly lengthen the refractory periods of both the slow and fast pathways, potentially making it difficult to induce tachycardia. A false-negative EP study due to suppression of conduction is most critical following RF ablation, when it may lead to recurrence of SVT.

Anesthetic effects have been best described for re-entry tachycardia. Isoflurane and halothane at one minimum alveolar concentration have been shown to cause prolongation of the APERP and it has been suggested that these agents should be avoided during ablation of accessory pathways [128]. A further study of isoflurane and a study of sevoflurane failed to demonstrate significant EP effects at one minimum alveolar concentration [129,130]. However, more recently, there has been a small-scale trial and a case presentation that have shown sevoflurane to increase APERP. In the case presented, this suppressed attempts to induce SVT despite pacing and isoproterenol [131,132]. Conversely, isoflurane and halothane prolong coupling interval, potentially increasing susceptibility to SVT. From animal studies it is clear that inhalational agents do have a number of EP effects in sufficient doses; however, the clinical significance of this (during EP study for pre-excitation syndromes) may be limited.

A number of clinical studies have demonstrated no direct effect of propofol on conduction at doses of 100–150 μg/kg/min other than possibly slight prolongation of atrial refractory period [129,133–135]. In studies on isolated hearts, significant EP effects are apparent only at concentrations unlikely to be achieved clinically.

Remifentanil at high-dose (0.4 μg/kg/min) and moderate-dose (0.2 μg/kg/min) dose infusions, when used with propofol-based anesthesia, prolongs the sinus node recovery time. High-dose infusion also suppresses sinus node automaticity [136]. Another study showed it had little effect on APERP, but did slow AV node conduction as well as SA node conduction [137]. This may cause problems with inducing tachyarrhythmias.

Midazolam and alfentanil in combination has been shown not to have direct effects on cardiac conduction [138]; however, they are impractical as sole agents for anesthesia. Droperidol produces a marked prolongation of APERP [139] and should be avoided. Vecuronium has no EP effects, but other neuromuscular blocking agents have not been studied.

Despite the EP effects of volatile and opioid agents, it will remain possible to induce SVTs due to re-entry in almost all patients when the mechanism of arrhythmia is pre-excitation. A technique utilizing low-dose opioids and a moderate dose of volatile agent is acceptable. High doses of volatile agents should be avoided. The successful use of total intravenous anesthesia with propofol for maintenance of anesthesia during an EP study for re-entry tachycardia has been described [140]. It remains uncertain whether the risk of false-negative studies is reduced in comparison to volatile anesthetics. Anesthesia may have more significant effects on the ability to induce tachycardia in AVNRT. Suggesting the superiority of any particular technique in this situation would be speculative.

Anesthetic drugs and automatic tachycardia

Ectopic (automatic) arrhythmia resulting from increased automaticity will behave differently under anesthesia. Many of the extrinsic factors, which promote automaticity, are minimized during steady-state anesthesia. Typically, catecholamine levels are low and cardiac work is decreased.

The direct effects of inhalational anesthetics on automaticity are complex. The abnormal behavior of these foci is related to an acceleration of spontaneous depolarization of the cell membrane. Halothane will reduce the rate of depolarization in SA cells, producing a predictable reduction in heart rate [141]. However, when uninjured Purkinje cells are exposed to halothane and epinephrine, the rate of spontaneous depolarization is increased [142]. The most likely substrate for tachycardia is injured Purkinje cells already demonstrating increased automaticity. It has been shown that these cells are not affected by volatile agents and their response to epinephrine is unaltered [142].

In a series of 150 patients with SVT anesthetized with propofol infusions, seven patients had arrhythmia due to...
ectopic atrial tachycardia [143]. The arrhythmia could not be induced in four of these patients despite infusion of isoproterenol. EP studies were successful in all of the 143 patients with re-entry tachycardia.

Given these data, it is difficult to suggest a best anesthetic technique for EP studies in patients with ectopic tachycardia. One approach is to limit the dose of volatile anesthetics during attempts to induce the tachycardia and to replace endogenous sympathetic activity with sympathomimetic drugs such as isoproterenol. The avoidance of general anesthesia can be considered in older patients.

Complications of EP studies
In a report of 2,761 EP studies, complications occurred in 87 patients (3.2%), most commonly hematoma at the site of vascular access [119]. Of the 2,672 patients who underwent ablation, complications occurred in 89 patients (3.3%). AV block occurred in 34 patients (1.3%) and was more common with AVNRT and accessory pathways close to the AV node. This broadly agrees with older reports. Mortality is rare. In the series mentioned there were no deaths, and no deaths have been reported among children in the UK during the last 3 years (Central Cardiac Audit Database data [1]) out of almost 800 procedures. Valvular regurgitation is rare (<0.5%) but can occur and coronary artery injury has been demonstrated in animal models of RF ablation [117].

Implantation of pacemakers and defibrillators
Pacemaker implantation is less common in children than in adults [144] and is indicated for complete heart block or for sinus node dysfunction leading to symptomatic bradycardia. Bradycardia may complicate CHD or surgery near the conduction pathways. Other indications include anti-tachycardia pacing for SVT, and placement of automatic defibrillator devices in long QT syndrome or late after tetralogy of Fallot repair with VT.

There are practical problems associated with the placement of pacemakers in small children. The pacemaker systems are relatively large, and thrombosis of central veins is a concern. It is difficult to accommodate for patient growth, and subcutaneous placement of the generator may be impossible (the abdomen is an alternative site). Epicardial wires are required in small infants and when access to the heart via the venous system is not possible (e.g., following the Fontan procedure).

Placement of epicardial wires requires a partial sternotomy and general anesthesia. Anesthesia may be associated with worsening of bradycardia. Treatment with isoproterenol may be instituted, followed by the rapid placement of a temporary pacemaker wire, or transthoracic or esophageal pacing. Transthoracic pacing is very disconcerting in the awake patient.

Implantation of defibrillators is indicated for life-threatening ventricular arrhythmia [145]. It is usual to test the defibrillator by induction of ventricular fibrillation and it is prudent to be prepared in case the device fails. Indications include isolated arrhythmia associated with long QT syndromes and patients with hypertrophic cardiomyopathy or arrhythmogenic right ventricular dysplasia who may have more general myocardial disease [146–148]. Often patients present after near-miss sudden death or death of a close family member and they and their families are often extremely anxious. Preoperative anxiety can be sufficient to induce arrhythmia, and premedication with an anxiolytic is advisable. There is a significant rate of inappropriate discharge of devices in young patients, as well as lead failure, presumably due to growth. CHD accounted for the majority of young patients with automated internal cardiac defibrillator in a single-center report in 2004 [149].

KEY POINTS: ELECTROPHYSIOLOGICAL STUDIES

- The majority of children presenting for EP investigation and treatment are otherwise healthy, have functionally normal hearts, and present with well-tolerated SVT.
- Knowledge of how anesthetic agents can alter the EP of the heart is vital to ensure false-negative studies do not occur.
- Mapping technologies are complex but allow greater accuracy of ablation of abnormal pathways or foci.

Conclusions
The trend towards more invasive therapeutic cardiac catheterization procedures in younger, smaller, and sicker patients increases the potential for hemodynamic and respiratory instability. As such, preparation and vigilance for these procedures by the anesthesiologist is essential. Approaching these procedures as if the patient were undergoing surgery will help to ensure the best outcome.

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http://www.wiley.com/go/andropoulos/congenitalheart

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CHAPTER 30
Anesthesia for Non-cardiac Surgery and Magnetic Resonance Imaging

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Introduction

The commonly reported incidence of congenital heart disease (CHD) in the United States is between 4 and 10 per 1,000 live births. The most common defects are ventricular septal defects, atrial septal defects, valvular pulmonary stenosis, tetralogy of Fallot, coarctation of the aorta, atrioventricular (AV) septal defects and transposition of the great arteries. The National Birth Defects Prevention Network data estimate that there are more than 6,100 cases annually of five defects in the US: truncus arteriosus, transposition of the great arteries, tetralogy of Fallot, AV septal defect, and hypoplastic left heart syndrome (HLHS). Annually, there are an estimated 9,200 patients requiring an invasive procedure related to CHD in the first year of life [1].

With improving survival, the number of unrepaired, repaired, and palliated children, teenagers and adults is increasing. With this increase in the number of patients living with CHD, there is a concomitant increase in the number of patients of all ages presenting for non-cardiac procedures requiring anesthetic care.

Data from the Pediatric Perioperative Cardiac Arrest (POCA) Registry report that there is a higher risk of perioperative cardiac arrest in children with CHD undergoing anesthesia compared with the rest of the pediatric population, and 54% of the arrests occurred during non-cardiac procedures. Mortality after cardiac arrest is also substantially higher for patients with cardiac disease, being 33% among those with heart disease, compared with 23% among those without. It is critical to recognize the patients at highest risk of anesthesia-related mortality: infants with single-ventricle lesions and patients with left ventricular outflow tract obstruction (LVOTO), cardiomyopathy or pulmonary hypertension [2,3].

The recognition of high-risk patient groups should lead to multidisciplinary discussion, selection of appropriate operative venue and recovery area, selection of anesthesia...
care provider, conduct of anesthesia and surgery, and level of monitoring – the goal is a reduction in morbidity and mortality.

**KEY POINTS: RISKS AND SEQUELAE IN CHD**

- There is a higher risk of perioperative cardiac arrest in patients with CHD.
- Mortality after cardiac arrest is higher for patients with CHD.
- The highest-risk lesions for anesthesia-related mortality are single ventricle, LVOTO, cardiomyopathy, and pulmonary hypertension.

**Preoperative preparation for non-cardiac surgery**

**Multidisciplinary planning**
Patients with CHD often have other congenital defects, most commonly orthopedic and urologic, and are often cared for by multiple specialists. Each patient most likely has a pediatrician, a cardiologist, and a cardiac surgeon. The patient may be referred to a general surgeon for a gastrostomy tube placement, a urologist for hypospadias repair, a dentist for dental cleaning and restoration, an orthopedic surgeon for treatment of limb deformities, and multiple other practitioners. In addition, the patient may be scheduled for magnetic resonance imaging (MRI) or computed tomography (CT) scanning to evaluate the cardiovascular system or another co-morbid organ system. Many, if not all, of these procedures require general anesthesia or sedation. The consulted services may not be aware of the patient’s anatomy, physiology, and risk associated with anesthesia. For patients at high risk, there should be a discussion between the primary services caring for the patient, the consulted service, and the anesthesia team to determine if the benefits of the procedure or study outweigh the risks. This team should determine where the procedure will take place, such as an outpatient operating room (OR) vs. an OR setup for emergent cardiopulmonary bypass, and how the associated risks can be minimized. The potential need for postoperative monitoring in an intensive care unit (ICU) should be discussed and planned in advance. Multidisciplinary planning is a crucial step in optimizing patient outcome.

This multidisciplinary approach can also result in anesthetic bundling, i.e., multiple procedures can be carried out under the same anesthetic. The patient may require fewer anesthetics and may be at a lower risk of potential anesthesia-related neurotoxicity, as well as anesthesia-related morbidity and mortality (see Box 30.1) [4].

**Box 30.1: The advantages of anesthetic bundling in patients with congenital heart disease**

- Decreased risk of potential anesthetic neurotoxicity (fewer exposures)
- Potential decrease in anesthetic related morbidity and mortality (fewer inductions, intubations, emergences, etc.)
- Less time nil per os
- Less time without cardiac medications such as anticoagulants, diuretics
- Improved patient/parent satisfaction

**Preoperative cardiology visit**

The timing of a preoperative cardiology visit prior to a non-cardiac procedure depends on the patient’s disease, the stage of repair or palliation, and the degree of limitation of activities of daily living (feeding, growing, neurodevelopment for infants; attending school for older children) due to cardiac disease. The type of non-cardiac procedure should not impact these guidelines, as a general anesthetic may be required for any procedure. In general, acyanotic patients who are repaired or who have no limitations due to cardiac disease do not require a preoperative cardiology consultation. If these patients have limitations and are not well compensated, a preoperative consultation is indicated within 6 months of the procedure. For patients with cyanotic CHD who are well compensated and have no limitations due to their cardiac disease, a cardiology visit within 12 months of the procedure is adequate. For patients with cyanotic CHD who have limitations due to their cardiac disease, a preoperative consultation is indicated within 6 months of the procedure.

Screening in a pre-anesthetic clinic setting to gather the results of imaging and other diagnostic studies and to review cardiology records is helpful. If necessary, a preoperative cardiology visit can be scheduled, additional tests, studies and consultations can be scheduled, and all data can be collected and reviewed prior to the patient’s arrival on the day of surgery. This step facilitates the selection of a properly experienced anesthesiologist as well as the proper setting for the anesthetic, and allows the anesthesiologist to prepare necessary medications and equipment in advance. A plan for the postoperative recovery site for the patient (post-anesthesia care unit [PACU] vs. ICU) should be made at this time. These preparations translate into fewer cancellations on the day of surgery.

**Interpretation of imaging and hemodynamics**

Preoperative imaging and hemodynamic studies are addressed extensively in Chapter 14. Important information obtained from imaging studies and cardiac catheterization include right and left ventricular function, presence of valvular stenosis or regurgitation, the size and...
direction of flow of atrial and ventricular septal defects, patency of shunts or vascular connections, and an estimate of pulmonary vascular resistance (PVR). These key pieces of information help to identify patients with lesions that place them at an increased risk for perioperative morbidity and mortality (e.g., cardiomyopathy, aortic stenosis, pulmonary hypertension) and to construct an anesthetic plan with appropriate hemodynamic goals.

**Nil per os**

Fasting times of 6 hours for solids or formula, 4 hours for breast milk, and 2 hours for clear liquids are the recommended guidelines from the American Society of Anesthesiologists and the European Society of Anaesthesiologists [5,6]. For patients with CHD, these fasting times are recommended as well. However, there are some important considerations in this patient population. Patients with LVOTO including hypertrophic obstructive cardiomyopathy, subaortic stenosis, aortic stenosis, and supravalvular aortic stenosis (Williams syndrome or non-Williams syndrome); systemic-to-pulmonary artery shunts (e.g., modified Blalock–Taussig shunt, ductal stent, central shunt); and polycythemic, cyanotic patients have an increased risk of perioperative morbidity and mortality when hypovolemic. Hypovolemic patients with LVOTO may develop significant hypotension during an inhalation induction with resultant decrease in coronary perfusion pressure that results in unresuscitatable cardiac arrest. Shunted patients with pulmonary blood flow that is completely dependent on systemic blood pressure may become profoundly hypotensive and hypoxemic on induction of anesthesia. Also, when there is decreased blood flow through the shunt, the likelihood of shunt thrombosis increases, as does an unfortunate cycle of hypotension and hypoxemia (Figure 30.1). Other polycythemic, cyanotic patients are at risk for thrombosis and stroke due to increased blood viscosity, which can be due to prolonged fasting. Hypovolemia due to fasting has been reported as a cause of periprocedural morbidity and mortality [7,8].

Prevention of hypovolemia is the key to minimizing this risk. Careful planning and communication will minimize the time these patients are without fluids. Families should be advised to give clear fluids liberaly until 2 hours prior to the procedure, and if the procedure is delayed, clear fluids can be administered by mouth at the hospital until 2 hours prior to the procedure. In addition, intravenous fluids can be started upon arrival in the hospital to replace losses before induction of anesthesia. Patients can also be admitted the night before surgery to receive intravenous fluids while fasting. These strategies decrease perioperative risk.

**Continuation of medications**

In general, all chronic cardiac medications should be continued perioperatively. Anticoagulants such as aspirin, warfarin, and heparin may be discontinued at the preference of the surgical team after discussion of a perioperative plan for stopping, transitioning, and restarting anticoagulation with the cardiology team. Another exception may be diuretic therapy. Continuation of diuretic therapy in a fasting patient may not be indicated. However, perioperatively, after volume administration, diuretic treatment may be warranted. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may also be held preoperatively due to a significant incidence of hypotension on induction of anesthesia in the general population [9,10]. These agents have also been associated with hypotension and hemodynamic instability on induction in pediatric patients with CHD undergoing non-cardiac operations [11].

**Endocarditis prophylaxis**

Congenital heart disease is the leading risk factor for infective endocarditis (IE) in children in the developed world. Lesions associated with increased risk of IE in children are cyanotic CHD, left-sided lesions, and endocardial cushion defects. In addition, the relative risk of developing IE is higher in the 6 months following cardiac surgery and in children less than 3 years of age [12]. The goal of IE prophylaxis is to provide appropriate antibiotic coverage for procedures that are associated with bacteremia. The three most common bacteria implicated in CHD-associated IE are *Streptococcus* (including *Streptococcus viridans*), *Enterococcus*, and *Staphylococcus* species [13].

The 2007 American Heart Association (AHA) guidelines for IE prophylaxis reduced the number of patients with CHD whom they recommend receive IE prophylaxis and reduced the number of procedures for which IE prophylaxis is recommended. The CHD patients for whom IE prophylaxis is recommended are those who have...
the highest risk of adverse outcome from endocarditis and these are listed in Box 30.2. Prophylaxis is recommended for patients who are within 6 months of complete repair with prosthetic material or a device. After 6 months, endothelialization of the prosthetic material has occurred, and IE prophylaxis is no longer recommended for these patients.

Infective endocarditis prophylaxis is recommended when both patient indications (Box 30.2) and procedure indications occur. For example, IE prophylaxis is recommended for all dental procedures that involve the manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa, but only for patients in Box 30.2. It is also recommended for patients in Box 30.2 who undergo invasive procedures of the respiratory tract that involve incision of the respiratory mucosa, such as tonsillectomy and adenoidectomy or bronchoscopy with biopsy. It is not recommended for bronchoscopy that does not involve incision of the mucosa. The antibiotic regimen should be active against viridans group Streptococcus (see Table 30.1). Antibiotic prophylaxis solely to prevent IE is not recommended for endoscopic gastrointestinal or genitourinary procedures that do not incise mucosa, i.e., uncomplicated endoscopies; if biopsies are taken then IE prophylaxis should be considered. However, if the patient is known to be infected or colonized, they should be treated with an antibiotic that covers Enterococcus [14].

**Key Points: Preoperative Preparation for Non-Cardiac Surgery**

- Multidisciplinary discussion is essential for determining the risk/benefit balance for a given procedure.
- Minimize fasting times, especially for patients at increased risk for hypotension and myocardial ischemia during induction of anesthesia.
- Consideration should be given holding certain cardiac medications on the morning of surgery, e.g., diuretics, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers.

**Table 30.1 Infective endocarditis prophylaxis for dental procedures in pediatric patients**

<table>
<thead>
<tr>
<th>Route</th>
<th>Drug and dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>Amoxicillin 50 mg/kg</td>
</tr>
<tr>
<td>Oral – penicillin/ampicillin allergic</td>
<td>Cephalexin 50 mg/kg or clindamycin 20 mg/kg or azithromycin or clarithromycin 15 mg/kg</td>
</tr>
<tr>
<td>Intravenous/intramuscular (IV/IM)</td>
<td>Ampicillin 50 mg/kg or cefazolin 50 mg/kg or ceftriaxone 50 mg/kg</td>
</tr>
<tr>
<td>IV/IM – penicillin/ampicillin allergic</td>
<td>Cefazolin 50 mg/kg or ceftriaxone 50 mg/kg or clindamycin 20 mg/kg</td>
</tr>
</tbody>
</table>

**Pacemakers and defibrillators**

The number of pediatric patients with cardiovascular implantable electronic devices (CIEDs), pacemakers and defibrillators, has increased as technology has advanced [15]. An increasing number of pediatric patients with these devices will likely present for non-cardiac as well as cardiac surgery. It is crucial to manage these devices properly to avoid injury, inappropriate shocking, and hemodynamic instability. A more extensive discussion of pacemaker and defibrillator therapy is presented in Chapter 18.

Preoperatively, it is important to understand the type of device in place, generator location, associated cardiac disease, indications for placement, and the remaining battery life. The underlying cardiac rhythm and degree of pacemaker dependence for cardiac output (none, partial, or complete) are key points of information. This information is best gleaned from a combination of history, physical exam, review of chest radiograph, discussion with or previous note from the cardiologist, and an interrogation of the device in the holding area by a CIED programmer (cardiologist, specialized nurse, or certified company representative from the device manufacturer).

Electromagnetic interference (EMI) in the OR is most commonly caused by monopolar electrocautery. EMI can result in inappropriate triggering or inhibition of pacing, reversion to asynchronous mode, inappropriate shock or anti-tachycardia therapy, and induction of current in the leads, resulting in myocardial damage. Strategies for reducing EMI include the use of bipolar instead of monopolar electrocautery, using short bursts of cutting rather than coagulation current when monopolar is required, and placing the grounding pad for the electrocautery far from the device site.

If EMI is likely during a procedure, the CIED programmer should reprogram the pacemaker to an asynchronous mode with a rate greater than the patient’s intrinsic rate. Similarly, the anti-tachycardia function of a defibrillator should be disabled until the risk of EMI is low. It is critical
to monitor the patient for a perfusing rhythm with either a plethysmographic or arterial line waveform, as well as electrocardiogram (ECG), after reprogramming. In addition, temporary pacing/defibrillation equipment must be available at all times, and the availability of appropriately sized equipment must be confirmed.

After the procedure when the risk of EMI is low, the device should be interrogated and reprogrammed back to its original baseline settings. It is critical to monitor for a perfusing rhythm and to have pacing/defibrillation equipment present until the device is reprogrammed [16–18].

A magnet can be used in an emergency situation to reprogram a CIED. It is not a substitute for interrogation/reprogramming by a CIED programmer, and it can have unpredictable consequences, particularly with modern multifunction pacemaker/defibrillator devices. For pacemakers, application of the magnet will usually change the pacemaker mode to an asynchronous mode (AOO, VOO or DOO – see Chapter 18) at a fixed rate, usually around 60–70 beats/minute (bpm). This fixed rate is device-specific and dependent on remaining battery life. Untoward effects of magnet application include pacing at a rate or in a rhythm that does not meet the patient’s metabolic or hemodynamic needs. For defibrillators, application of the magnet usually suspends the anti-tachycardia function, but does not change the pacemaker to an asynchronous mode. If the patient experiences ventricular tachycardia or ventricular fibrillation while the magnet is applied, the magnet should be quickly removed so that the anti-tachycardia function is restored and the device can deliver a shock [17]. This restoration does not occur with all systems, however; some are disabled until interrogation/reprogramming occurs [19]. There is no substitute for consultation with an expert, assessing the function of the device and converting the functions to an appropriate intraoperative mode. Obviously, there may be emergency situations where this will not be possible. The critical importance of monitoring the patient for a perfusing rhythm throughout the procedure, having backup pacing/defibrillation equipment present, and interrogating and reprogramming the device postoperatively cannot be overemphasized. There is a discussion of MRI-compatible pacemakers later in the chapter.

**KEY POINTS: PACEMAKERS AND DEFIBRILLATORS**

- Preoperatively, all CIEDs should be interrogated and potentially reprogrammed by the CIED service.
- After reprogramming, the patient must be monitored for a perfusing rhythm with an arterial line or plethysmographic waveform.
- Magnet application can have unpredictable consequences and should not be used as a substitute for interrogation and reprogramming.

**The patient on ventricular assist device support**

Heart failure most commonly resulting from CHD, cardiomyopathy, and myocarditis is the diagnosis associated with more than 12,000 annual pediatric hospital admissions in the United States [20]. Most of these patients can be managed medically or surgically, but there are a growing number of pediatric patients that require extracorporeal membrane oxygenation (ECMO) or ventricular assist device (VAD) placement. There are now devices that are appropriate for all sizes of pediatric patients for long-term support (see Table 30.2) [21,22]. These devices are discussed in detail in Chapter 31.

After placement, cardiac output can be maintained for these patients until cardiac function recovers or a suitable organ becomes available for transplant. In some cases, the patient can remain on VAD support indefinitely, as destination therapy. Destination therapy has been described in patients with end-stage heart disease due to muscular dystrophy [23]. These patients on long-term VAD support will likely require anesthesia or sedation for multiple imaging procedures and non-cardiac interventions and procedures. In order to provide care for this population of patients, one should become familiar with the different types of devices and the management of hypotension, hypertension, and a decrease in output. A perfusionist or VAD-trained nurse should be present for all non-cardiac procedures to assist with management and transport of the device. In addition, bacterial endocarditis prophylaxis is warranted in all VAD-supported patients.

**Table 30.2** Long-term ventricular assist device options for pediatric patients

<table>
<thead>
<tr>
<th>Device</th>
<th>Positioning</th>
<th>Flow type</th>
<th>BSA (m²)</th>
<th>Ambulation</th>
<th>Discharge home</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berlin EXCOR®</td>
<td>Paracorporeal</td>
<td>Pulsatile</td>
<td>0.2–1.3</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Thoratec®</td>
<td>Paracorporeal</td>
<td>Pulsatile</td>
<td>&gt;0.7</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Heart Mate ll®</td>
<td>Intracorporeal</td>
<td>Axial</td>
<td>&gt;1.4</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>HeartWare®</td>
<td>Intracorporeal</td>
<td>Axial</td>
<td>&gt;0.7</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

BSA, body surface area.

Source: Mossad et al. [21]. Reproduced with permission of Wiley.
The Berlin EXCOR® (EXCOR® Pediatric Ventricular Assist Device, Berlin Heart, GmbH, The Woodlands, Texas, USA) is a pneumatically driven pump that generates a pulsatile pressure with a rate between 30 and 150 bpm depending on the size of the pump chamber and the size and needs of the patient. The transparent pump chamber allows for visual evaluation of filling, emptying, and thrombus formation. Because of the range of pump sizes, it can be used in neonates, infants, and children, and it is the device that is used most commonly for long-term support in pediatric patients at the present time [22].

Anesthetic management of the patients with a Berlin EXCOR® device requires familiarity with the pump and how to troubleshoot hypotension, hypertension, and reduced output. Cave et al. describe a 69% incidence of hypotension in a case series of 29 non-cardiac procedures on 11 patients with a Berlin EXCOR® device [24]. This group found that hypotension on induction was most associated with the use of remifentanil and was least associated with the use of ketamine as an induction agent. Care should be taken with the administration of anesthetic agents associated with a decrease in systemic vascular resistance (SVR), and intravascular volume and vasoactive agents that increase SVR should be on hand [24].

When caring for a patient with a Berlin EXCOR® device, it is critical to maintain the ability to visually inspect the pump. This may require clear drapes, a mirror, and a flashlight. The membrane should be inspected regularly to check for fibrin deposition and for membrane wrinkling. Membrane wrinkling is a sign of incomplete filling of the chamber. Device inspection is a key component of determining the cause of hypotension and the appropriate treatment. Table 30.3 illustrates the utility of pump chamber inspection on treatment of hypotension and hypertension [21].

Intraoperative emergencies in a patient with a Berlin EXCOR® include malignant dysrhythmias, sudden loss of cardiac output, the appearance of air or clot in the pump chamber, and sudden cyanosis. If the patient develops a dysrhythmia, the pump should be examined for filling and output. The right ventricle (RV) can act like a conduit in the short term, and VAD output can be maintained. External compressions are contraindicated. The patient may require external cardioversion. Loss of cardiac output is most commonly associated with an alarm from the Berlin EXCOR® driver unit. It is most commonly caused by a kink in the external tubing of the device. The device should be examined and the tubing uninked. Appearance of air or clot in the pump chamber can signal an impending embolism. A cardiac surgeon and a perfusionist should be called to the bedside for an urgent pump exchange. Sudden cyanosis in a patient with a Berlin EXCOR® device may be a sign of pulmonary embolism with right-to-left shunting through an interatrial communication. Transthoracic echocardiography can aid in diagnosis [25].

The condition of an unsupported right heart cannot be overlooked in the patient with an unsupported assist device (LVAD). Perioperatively, hypoventilation associated with hypoxemia and hypercarbia can result in right ventricular failure. In the patient with an LVAD, this is manifest by decreased output and incomplete filling of the device [26]. A decline in right heart function should always be in the differential diagnosis of poor cardiac output, and maneuvers to improve right ventricular function should be instituted early. These maneuvers include the avoidance of hypoxemia and hypercarbia, inotropic support, and the use of inhaled nitric oxide.

### Table 30.3 EXCOR® pump chamber inspection, diagnosis and management

<table>
<thead>
<tr>
<th>Hemodynamic Change</th>
<th>Device Inspection</th>
<th>Etiology</th>
<th>Potential Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>Membrane wrinkling during diastole (incomplete filling)</td>
<td>Hypovolemia</td>
<td>Fluid bolus (10 mL/kg) Augment RV function and decrease PVR Increase SVR with phenylephrine or vasopressin</td>
</tr>
<tr>
<td></td>
<td>Complete filling observed</td>
<td>Vasodilation</td>
<td>Sedation, deepen anesthetic</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Membrane wrinkling during systole (incomplete ejection)</td>
<td>Pain, anxiety, awareness</td>
<td>Decrease SVR with nitroprusside or nicardipine</td>
</tr>
</tbody>
</table>

RV, right ventricle; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance.

Source: Mossad et al. [21]. Reproduced with permission of Wiley.
Management strategies for the stages of single-ventricle palliation

The single-ventricle surgical palliation pathway is presented in detail in Chapter 25. An understanding of the anatomy and physiology and familiarity with basic hemodynamic and ventilatory management strategies for the different stages of single-ventricle palliation are important for the successful care of these patients in the non-cardiac OR and radiology suite (see Table 30.4). Instability should be anticipated at any stage of single-ventricle palliation, and vasopressors, inotropes, defibrillation capability, and volume expanders should be readily available. In addition, these patients are frequently cyanotic and thus are dependent upon chronically increased red cell mass for oxygen delivery to tissues; packed red blood cells should be available (type and screen or type and cross-match) to transfuse for most surgical procedures. A hematocrit of 40–45% is recommended for cyanotic and shunt-dependent neonates and infants to maintain oxygen-carrying capacity. The superior cavopulmonary anastomosis or Glenn stage of single-ventricle palliation is generally associated with more resilient physiology. The patient is no longer shunt-dependent, the volume burden on the single ventricle is reduced, and cardiac output is not solely dependent on passive pulmonary blood flow as in the Fontan circulation. If possible, elective non-cardiac surgery should take place during this stage [4,27,28].

<table>
<thead>
<tr>
<th>Stage of palliation</th>
<th>Cardiac lesion</th>
<th>Surgical palliation</th>
<th>Pathophysiological considerations</th>
<th>Anesthetic considerations after palliation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal</td>
<td>Hypoplastic left heart syndrome</td>
<td>Norwood stage I palliation</td>
<td>Systemic and pulmonary output both ejected by functional single ventricle; pulmonary to systemic vascular resistance ratio determines cardiac output</td>
<td>Avoid hypoxemia and hyperventilation; maintain sinus rhythm, and cardiac contractility</td>
</tr>
<tr>
<td>Infants: cavopulmonary connection</td>
<td>Any single-ventricle lesion</td>
<td>Superior cavopulmonary connection (bi-directional Glenn operation)</td>
<td>Cerebral-pulmonary-cardiac circulation is predominant in younger infants</td>
<td>Avoid hyperventilation; most stable stage for elective non-cardiac surgery</td>
</tr>
<tr>
<td>Fontan completion</td>
<td>Any single-ventricle lesion</td>
<td>Total cavopulmonary connection (Fontan operation)</td>
<td>Positive pressure ventilation decreases venous return and cardiac output; intolerant of hypovolemia or non-sinus rhythm</td>
<td>Minimize positive pressure ventilation; maintain ventricular volume, sinus rhythm, myocardial contractility; perform elective non-cardiac surgery before this stage when possible</td>
</tr>
</tbody>
</table>

Source: Gottlieb & Andropoulos [4]. Reproduced with permission of Lippincott, Williams & Wilkins.
**Shunt-dependent single-ventricle patients**
These patients have a systemic-to-pulmonary arterial shunt that creates a volume burden on their single ventricle from the parallel pulmonary and systemic circulations. They have a reduced oxygen-carrying capacity, and their normal oxygen saturation is 75–85%. They also have reduced diastolic pressure from the run-off of blood into the low-resistance pulmonary circulation through the systemic arterial to pulmonary artery shunt. Instead of a systemic-to-pulmonary artery shunt, many shunted single-ventricle infants will have a right (systemic) ventricle-to-pulmonary artery shunt (Sano shunt). Although theoretically more stable because diastolic blood pressure is usually higher, similar pathophysiological considerations apply, and there are insufficient data reporting outcomes of non-cardiac procedures to determine that this shunt lowers the risk of anesthesia. The approach should be the same for all shunted single-ventricle infants before the bi-directional cavopulmonary connection.

This physiologic combination leaves them particularly vulnerable to hemodynamic insults, and a mild reduction in blood pressure may produce myocardial ischemia. Up to 16% of patients with HLHS who survive the Norwood procedure and are discharged home die prior to their second stage of palliation, which is a reflection of their fragile circulation [29]. These patients frequently have feeding difficulties, and a number of them will undergo gastrosomy tube placement. Slater et al. described good outcomes among 12 patients with HLHS (nine after stage 1 reconstruction, three after stage 2) [30]. At our institution, even minor non-cardiac procedures on shunted single-ventricle patients are performed in the cardiac ORs, and the patients are admitted to the cardiovascular ICU for postoperative care and monitoring.

The hemodynamic condition is optimized by avoiding myocardial depressants and vasodilators. Diastolic hypotension may develop from the use of high inspired oxygen concentration or hyperventilation due to a reduction in PVR. The anesthesiologist should attempt to maintain the oxygen saturation near the patient’s baseline. This is accomplished primarily through the adjustment of minute ventilation. The inspired oxygen concentration is usually maintained close to room air. In addition, hematocrit should be maintained at approximated 45% to maximize oxygen-carrying capacity.

**Palliated single-ventricle patients with AV valve regurgitation**
After the second and third stages of single-ventricle palliation (Glenn and Fontan), the vast majority of patients have good cardiac reserve. The volume burden on the ventricle is greatly reduced during the second stage of palliation, and despite remaining cyanotic, myocardial performance improves. Trivial to mild AV valve regurgitation is observed by echocardiography in essentially all single-ventricle patients. However, patients with moderate to severe AV valve regurgitation commonly have a dilated valve annulus and reduced cardiac output. AV valve regurgitation reduces the forward flow of blood and causes the heart to dilate. In this situation, the hemodynamic status is optimized by reducing afterload and maintaining a normal or slightly increased heart rate. Typically, the myocardial depressant effects of even low doses of inhalation anesthetics are poorly tolerated.

**Pulmonary hypertension with systemic or supra-systemic PA pressure**
This condition is a well-recognized risk factor for perioperative morbidity and mortality. Recent publications report a significantly higher incidence of intraoperative cardiac arrest and death among patients with supra-systemic PA pressures. In a report of 101,500 pediatric anesthetics, of the 10 patients at the Royal Children’s Hospital in Melbourne whose death was related to anesthetic management, 50% had pulmonary hypertension [3,31]. Pulmonary hypertensive crisis is defined by a sudden increase in PVR that results in the PA pressure exceeding mean arterial pressure. This will compromise systemic cardiac output because reduced right ventricular output decreases left heart filling, and RV dilation shifts the interventricular septum leftward, which further impedes LV filling and ejection. Lower blood pressure with increased myocardial oxygen demands leads to right ventricular ischemia. Cardiac arrest rapidly follows.

First-line treatment includes increasing the inspired oxygen concentration to 100%, reducing PaCO₂, increasing the pH (alkalinization), and initiating inhaled nitric oxide. Hypotension should be treated with phenylephrine or vasopressin to increase coronary perfusion pressure. Epinephrine may also be given to improve cardiac output. Overly aggressive manual ventilation should be avoided because the increase in intrathoracic pressure may reduce venous return, therefore further compromising cardiac filling. The pulmonary vasculature is responsive to changes in pH, and alkalinization with sodium bicarbonate or tromethamine (THAM) can be effective in reducing pulmonary pressures. Some authorities recommend prophylactic preanesthetic administration of inhaled nitric oxide for high risk patients with pulmonary hypertension.

It should also be recognized that the perioperative risk of these patients extends into the post-anesthesia recovery period. These patients must be closely monitored, and conditions that increase PVR should be avoided, including hypoxemia, hypercarbia, pain, agitation, and acidosis [32]. See Chapter 28 for a complete discussion of pulmonary hypertension.

**Severe aortic stenosis (peak gradient > 60 mmHg)**
The pressure burden from aortic stenosis causes the ventricle to hypertrophy, but not dilate. Therefore, ventricular function is generally well maintained even with a significant degree of stenosis. These children usually have normal exercise tolerance and appear normal to their families. However, the hypertrophied ventricle is
at risk for developing ischemia if the patient becomes hypotensive. If the diastolic blood pressure decreases, as it commonly does during a routine inhaled induction, the ventricle may become ischemic. Bradycardia and/or ST-segment changes may be evident on the ECG. If myocardial ischemia progresses to cardiac arrest, closed cardiac compressions are generally ineffective because of the aortic valve stenosis. As these patients may be sensitive to hypotension, an α-agonist such as phenylephrine must be immediately available and used early if diastolic blood pressure decreases or myocardial ischemia is suspected from a change in the ECG.

Care should be taken to avoid hypotension on induction of anesthesia for these patients. Hypovolemia can lead to an exaggerated decrease in blood pressure with induction. Thus, excessive fasting times should be avoided. Clear liquids should be given up until 2 hours prior to the procedure. Intravenous fluids may be started the night before or upon arrival to the day surgery unit to maintain euvolemia. A careful intravenous induction may be preferred for these patients. Medications can be titrated gradually to avoid a decrease in blood pressure, and α-agonists can be administered during induction as needed. Monitoring with an arterial catheter placed prior to induction or soon thereafter may be helpful. Chapter 22 presents a thorough discussion of this lesion and other forms of LVOTO (Williams syndrome, hypertrophic cardiomyopathy; see the following sections).

**Williams syndrome**

Up to two-thirds of patients with Williams syndrome develop supravalvular aortic stenosis. The outflow tract obstruction frequently arises as a concentric narrowing of the ascending aorta at the superior margin of the sinuses of Valsalva, creating a typical hourglass deformity. This is caused by a defect in the elastin gene, resulting in a deficiency in this crucial connective tissue protein. These patients may also have diffuse narrowing along the entire length of the aorta, and their arteriopathy may also include the coronary arteries. Obstruction of the left coronary artery, reduction in the size of the ostia, and diffuse coronary artery narrowing have all been described, even in the absence of significant supravalvular aortic stenosis. This syndrome is associated with sudden death upon induction of anesthesia. Proper preparation, including avoidance of excessive fasting and preoperative hypovolemia, is critical. Similar to the patient with aortic stenosis, diastolic hypotension is not well tolerated and should be aggressively treated. Resuscitation after cardiac arrest may not be possible [33].

The authors believe that the anesthesia consent process should involve a discussion of the patient’s risk for perioperative cardiac arrest. Many parents of children with Williams syndrome are aware of the risk of sudden death; it is important for the parents to recognize that the anesthetic and perioperative team is also aware of the risk and is adequately prepared.

**Hypertrophic cardiomyopathy**

Children with hypertrophic cardiomyopathy have an annual mortality rate of approximately 1%, if they survive beyond 1 year of age. Like aortic stenosis, these children often have few symptoms, but are also at risk for worsening of their LVOTO with hypovolemia, tachycardia, and increased contractility. Some patients, e.g., those with Noonan syndrome, may manifest biventricular obstruction. The hemodynamic goals are to maintain preload, maintain afterload, avoid tachycardia, and reduce contractility. The ECG should be monitored closely, and ST changes should be treated with an α agonist [34,35].

**Pulmonary atresia and intact ventricular septum**

One-third to two-thirds of patients with pulmonary atresia and intact ventricular septum (PA/IVS) have endothelial-lined blind channels within the right ventricular myocardium, known as sinusoids. These sinusoids are in direct communication with the cavity of the RV and can form coronary artery to RV fistulae. These fistulae send desaturated blood to the myocardium of the RV. An RV-dependent coronary circulation is reported in 3–34% of patients with PA/IVS. In this situation, a considerable portion of the left ventricle is supplied by fistulae. The myocardium of these patients is typically strained at baseline and increases in myocardial work, or a reduction in myocardial oxygen supply will produce ischemia. When these patients have a systemic-to-pulmonary arterial shunt, they are at a higher risk of ischemia due to an increase in volume work and a decrease in diastolic blood pressure due to the shunt [36]. Preload and afterload should be maintained, tachycardia should be avoided, and administration of myocardial depressants should be minimized. Chapter 23 has an extensive discussion of this lesion.

**Transplant coronary artery disease**

The incidence of transplant coronary artery disease (TCAD) in pediatric patients is 17% at 5 years after cardiac transplantation, and 24% of patients with any degree of TCAD died within 2 years in a recent report. A multi-institutional study found that the major risk factors for TCAD were older recipient age and donor > 30 years of age [37]. Symptoms of TCAD are atypical due to the denervation of the transplanted organ. However, the symptom complex of abdominal, chest, and/or arm pain should raise suspicion [38]. These patients should have routine cardiac catheterization with coronary angiography, and the anesthesiologist should consider all heart transplant patients to be at risk, even patients who have had normal coronary angiography in the past. This risk increases with greater time after transplant. Excessive decreases in coronary perfusion pressure should be avoided, the ECG should be carefully monitored for signs of ischemia, and hypotension should be treated early with α-agonists. See Chapter 27 for further discussion of this entity.
Eisenmenger syndrome

Eisenmenger syndrome is fortunately rarely seen in this era. In our institution, most children who have developed Eisenmenger syndrome have recently emigrated from a country where indigent patients do not have access to pediatric cardiovascular surgery. Similar to pulmonary hypertension, these patients have a reactive pulmonary vasculature and should be managed similarly.

KEY POINTS: HIGH-RISK PATIENT GROUPS

- Patients with pulmonary hypertension are at an increased risk of morbidity and mortality intraoperatively; it must be recognized that this risk extends into the postoperative period.
- Patients with Williams syndrome may have coronary artery abnormalities in the absence of significant supravalvular aortic stenosis that put them at increased risk for myocardial ischemia.
- The ECG should be monitored closely for signs of ischemia in high-risk patients; ST changes should be promptly addressed.

Intraoperative care

Monitoring

Standard American Society of Anesthesiologists (ASA) monitors provide adequate monitoring for the vast majority of children undergoing less invasive surgical or diagnostic procedures. When caring for healthy children who may be fearful of placing the ECG pads and non-invasive blood pressure (NIBP) cuff, it is common practice to apply these monitors after the initiation of an inhalation induction. Children with CHD should have baseline vital signs before induction, and increasing the frequency of NIBP determination from the default of once every 3 minutes should be considered. High-risk patients, such as those described in the previous section, or patients undergoing major orthopedic, intra-abdominal, or intrathoracic procedures are best managed with invasive arterial monitoring and/or central venous monitoring. Invasive arterial monitoring will assist in the early recognition of hypotension, and arterial blood gas monitoring allows easy determination of acid–base status, electrolytes, and hemoglobin. There are many cardiac lesions that are sensitive to a reduction in preload, yet these same patients may manifest a reduction in pulmonary compliance with volume overload. In this situation, central venous monitoring is very useful and provides good vascular access for the delivery of vasoactive medications.

There are a number of newer monitors designed to measure cardiac output non-invasively. Some of these monitors have been validated against thermodilution or echocardiographic measurements of cardiac output. However, none of these new monitors have been shown to provide an early warning of a low cardiac output state that improves recognition and outcome. Near-infrared spectroscopy (NIRS) has been most widely studied. This monitor measures oxygen saturation of tissue approximately 2–4 cm beneath the probe. It was originally designed to determine cerebral oxygen saturation in the frontal cortex when the probe is applied to the forehead. It provides a non-invasive assessment of the regional oxygen supply–demand balance to the tissues over which the probe is applied (brain, kidney, gut). It is affected by tissue blood flow, arterial oxygen saturation, hemoglobin saturation, and the ratio of arterial to venous blood flow. These factors should be considered when interpreting changes in tissue oxygen saturation. As a continuous monitor, it has been shown to identify global hypoperfusion produced by a reduction in cardiac output due to a reduction in mixed venous oxygen saturation [39]. The monitor has been used to detect splanchic ischemia in premature infants [40]. NIRS monitoring has also been shown to provide an early indication of reduced cardiac output after cardiac surgery [41]. It may therefore be a useful addition to routine non-invasive monitors for the child with CHD who has a greater risk of hemodynamic compromise, by providing an early warning and enabling a rapid response. However, no studies have determined the monitor’s utility and ability to improve outcomes in the setting of non-cardiac surgery. See Chapter 10 for a further discussion of monitoring techniques.

Anesthetic technique

The choice of anesthetic technique depends on the anticipated duration and the hemodynamic consequences of the planned surgery, the hemodynamic consequences of the patient’s cardiac anatomy, and the patient’s cardiac reserve. In general, patients with CHD are not tolerant of the myocardial depressant effects of higher concentrations of inhalational agents. Opioids are used to reduce the requirement of inhalational agent. See Chapter 6 for a discussion of the hemodynamic effects of anesthetic agents, and Chapter 17 for a discussion of hemodynamic management.

Regional anesthesia is not contraindicated unless the patient is taking anticoagulant medication, and regional anesthesia will allow a reduction in volatile agent requirement without the side-effects of opioid medications. Most patients have improved cardiac output from the sympathectomy that develops from central neuraxial blocks; the exceptions are the patient with aortic or mitral stenosis and those with obstructive cardiomyopathy.

Surgery

Many less invasive surgical procedures can be performed on an outpatient basis, even for ASA 3 and 4 patients. However, all high-risk patients should undergo surgery in a location where appropriate rescue can be performed. Even though complications are rare, the incidence of
cardiac arrest or death is significantly greater among patients with CHD, and most surgetcenters do not have appropriate rescue capability for these patients. Special consideration should be made for the high-risk population outlined earlier, and they should undergo non-cardiac surgery in a location where rhythm disturbances are rapidly recognized and treated, resuscitative medications are present, and rescue with ECMO is available. When dealing with patients with systemic or supra-systemic pulmonary hypertension, inhaled nitric oxide should be immediately available to treat acute increases in pulmonary pressure.

Complex surgical situations
Laparoscopic surgery
Laparoscopic surgery has many benefits, including smaller incision, faster return of bowel function, decreased postoperative pain, and shorter hospital stays. This technique requires insufflation of carbon dioxide into the peritoneum. There has been concern that patients with CHD might not tolerate the hemodynamic effects of abdominal insufflation. For example, the pulmonary blood flow of shunted single-ventricle patients is dependent on PVR. The pneumoperitoneum can result in decreased ventilation due to increased intra-abdominal pressure with an associated increase in PaCO₂, absorption of carbon dioxide with an associated increase in PaCO₂, a decrease in preload and an increase in SVR. It should be noted that end-tidal CO₂ has been shown to be an inaccurate measure of PaCO₂ in patients with cyanotic CHD [42]. However, with close monitoring of blood gases and ventilator adjustments, low insufflation pressures of 8–12 mmHg, and blood pressure support, outcomes can be optimized [30,43]. In must also be remembered that many CHD patients have right-to-left intracardiac shunts from septal defects or complete intracardiac mixing; a large CO₂ embolus into the systemic arterial circulation (coronary and cerebral) can rapidly cause cardiovascular collapse or neurological injury in these patients.

The patient with a Fontan circulation requires adequate preload and normal PVR to maintain passive pulmonary blood flow. Concerns regarding a decrease in pulmonary blood flow due to the combination of positive pressure ventilation and abdominal insufflation, as well as an increase in PVR due to carbon dioxide absorption, make laparoscopic surgery appear higher risk in these patients. However, there have been several case reports and small case series noting stable hemodynamics with laparoscopic surgery in Fontan patients with good ventricular function, without the need to augment preload or administer vasoactive medication [44,45]. For short procedures such as laparoscopic appendectomy or cholecystectomy, arterial and central venous pressure (CVP) monitoring has not been needed. As this experience is altogether small, we recommend discussing the potential need to convert to an open procedure with the surgeon, patient, and/or family prior to surgery. In addition, insufflation should be gradual and the minimum intra-abdominal pressure utilized.

Hemodynamic changes with the release of pneumoperitoneum should also be anticipated. Studies in healthy children have shown that the release of pneumoperitoneum results in a decrease in SVR and blood pressure, and a decrease in preload due to redistribution of blood into the splanchic bed and liver [46–48]. Groenewald and Latham report a cardiac arrest in a patient with supravalvular aortic stenosis immediately following release of pneumoperitoneum. It is suggested that patients, especially those at risk for myocardial ischemia, be monitored closely during this period, and that the release of intra-abdominal pressure be gradual [49].

Direct laryngoscopy and bronchoscopy
The procedure of direct laryngoscopy and bronchoscopy is very stimulating, generally requires spontaneous ventilation, and is therefore associated with hypoventilation. Patients who are at greatest risk with this procedure include those with cyanotic lesions, those with pulmonary hypertension, and those with poor myocardial reserve. Whatever anesthetic technique is chosen, the anesthesiologist must maintain close communication with the otolaryngologist, and primary and secondary plans for managing the airway should be discussed before the procedure. Even though most otolaryngologists prefer spontaneous ventilation during rigid bronchoscopy, it is typically only required to assess vocal cord mobility. Once that portion of the examination is complete, the patient can potentially receive muscle relaxant and positive pressure ventilation, and the depth of anesthesia can be reduced. Positive pressure ventilation can be supported via a jet port incorporated into the surgeon’s laryngoscope and then via the bronchoscope, or with intermittent tracheal intubation by the surgeon.

Spinal instrumentation
Patients with a prior thoracotomy are at greater risk of requiring spinal instrumentation surgery to correct scoliosis, and therefore CHD patients may require this invasive procedure. Spinal cord monitoring is routinely used and includes somatosensory evoked potentials and transcranial motor evoked potentials. Volatile anesthetic agents including nitrous oxide interfere with spinal cord monitoring and most patients require a total intravenous technique to obtain good signals. Propofol is generally used along with a continuous infusion of short-acting opioids such as remifentanil, sufentanil, or fentanyl. This surgery is performed in the prone position and is commonly associated with significant blood loss; both of these situations may be poorly tolerated in a patient with CHD who has limited cardiac reserve. Invasive arterial blood pressure monitoring is standard, and patients with CHD will generally benefit from continuous CVP monitoring, and potentially continuous venous saturation monitoring. A few case series have reported successful surgeries; however, blood loss is commonly greater (secondary to
KEY POINTS: INTRAOPERATIVE CARE

- Monitoring, anesthetic technique, and operative venue are dependent on the patient’s disease and the procedure performed; hemodynamic instability should be anticipated.
- The hemodynamic effects of the creation and release of pneumoperitoneum should be anticipated; gradual, low-pressure insufflation and gradual release produce the least disturbance.
- Laparoscopic procedures can be safely performed in patients with CHD, provided there is meticulous attention to hemodynamic and ventilatory management by experienced providers.

Magnetic resonance imaging and computed tomography

Anesthetic care is often required for diagnostic imaging of the patient with CHD, as patient immobility is frequently required for an adequate study. Cardiac magnetic resonance (CMR) and CT imaging of patients with CHD can provide valuable information about anatomy and function. MRI studies of the brain are commonly used to evaluate preoperative or postoperative neurologic abnormality or injury. The approach to reducing mobility for these studies varies from no anesthetic or sucrose, to sedation, to general anesthesia with spontaneous ventilation, to a general anesthetic with breath-holding. It is important to discuss requirements of the study with the radiologist and choose an appropriate plan based on the requirements and patient factors. The choice of CMR or CT imaging depends on the information desired, the potential need for general anesthesia, and the patient’s perceived anesthetic risk vs. risk of radiation exposure.

Cardiac magnetic resonance imaging can provide information regarding extracardiac arteries and veins, assessment of vascular or valvular flow, quantification of shunts, and assessment of myocardial function. It is the imaging modality of choice for the evaluation of corrected tetralogy of Fallot, aiding in the determination of timing for pulmonary valve replacement by the measurement of right ventricular volumes. It can also be used for pre-Glenn or pre-Fontan evaluation of single-ventricle patients in lieu of cardiac catheterization [55,56]. Risks associated with catheterization, including vascular injury and cardiac tamponade, are removed, and patients are not exposed to ionizing radiation. Compared with diagnostic cardiac catheterization, imaging with CMR is associated with a decreased length of hospital stay [57]. CMR is also the imaging modality of choice for complex aortic coarctations that require further arch delineation [55]. CMR can also be performed to gather information regarding myocardial perfusion at rest and with stress using adenosine or dobutamine. CMR also has a role in diagnosing cardiomyopathies, even in pre-clinical stages [58].

Although there is associated exposure to ionizing radiation, cardiovascular CT is especially useful in imaging for vascular rings, where it is important to visualize related airway anatomy, pulmonary venous anatomy, or major aortopulmonary collateral arteries (MAPCAS), and in patients with metallic implants or CIEDs [58]. CT can also be used to evaluate coronary artery anomalies. Advances in CT technology and the introduction of second-generation, dual-source, high-pitch scanners have resulted in cardiovascular imaging that is associated with a significant decrease in exposure to ionizing radiation (equivalent to approximately five chest radiographs for most studies), faster scans, and an elimination of the need for breath-holding. For a significant number of patients, this obviates the need for a general anesthetic [59]. See Chapter 14 for a further discussion of the utility of CMR and CT imaging.

Anesthetic techniques for these imaging studies vary in the depth and degree of airway manipulation. On the least invasive end of the spectrum, a feed and swaddle technique using a natural airway can be used for CT and shorter MR studies in neonates and young infants. Neonates have undergone cardiac CT angiography using a non-sedated, free-breathing, swaddling technique with excellent image quality [59]. Fogel et al. describe the successful CMR evaluation of aortic arch anomalies using this technique in infants less than 6 months of age. The CMR scanning time in this study was 6.2 ± 3.1 minutes [56]. The success of this strategy hinges on the presence of a cardiac imaging specialist in the control room to evaluate the images as each sequence is completed, and expeditious, efficient scanning that focuses on the diagnostic question.

Children are unlikely to stay still for a longer study without deep sedation or general anesthesia. Many centers employ deep sedation or general anesthesia via intravenous medications while maintaining a natural airway and spontaneous respiration. Medications used for this purpose include propofol infusion, dexmedetomidine infusion, and an infusion of a combination of propofol and ketamine. It is important to monitor the ECG, oxygen saturation, blood pressure, and end-tidal CO₂ during the sedation. End-tidal CO₂ can be monitored via a nasal
cannula with a CO₂-monitoring port or through a port placed in a face mask.

Airway monitoring during the procedure is important, as airway obstruction can occur with general anesthesia or sedation. Airway compromise leading to increased PaCO₂ and/or decreased PaO₂ is poorly tolerated in some patients, especially those with pulmonary hypertension. These types of patients must be carefully monitored for developing hypercarbia and hypoxemia. A general endotracheal anesthetic is another option for longer procedures or when the airway control is crucial. In addition, it is possible to hold respiration for certain sequences. Another option includes a general anesthetic with a laryngeal mask airway.

The need for breath-holding when carrying out CMR varies according to the structures being imaged, the programmed sequences, and the experience and preference of the imaging team. The need for breath-holding increases as the size of the structures being imaged gets smaller. As many as eight breath-holds of 10–30 seconds are required for some diagnostic scans; the pathophysiological effects of this technique must be considered, i.e., the effect of preoxygenation and the lack of ventilation on shunted single-ventricle infants. Su et al. described an ECG and respiration-gated technique that obviates the need for breath-holding in the great majority of CMR studies. This technique allows selection of sedated, spontaneously breathing techniques for many patients [60].

It is critical to match the patient’s cardiac lesion and cardiac function with an appropriate anesthetic. For example, a single ventricle with a modified Blalock–Taussig shunt is unlikely to tolerate a deep sedation with propofol. Propofol may lead to a decrease in mean arterial pressure, a decrease in driving pressure through the shunt, and an increase in PVR due to hypoxemia and hypercarbia from hypoventilation. This can result in a further decrease in shunt flow and dangerously low oxygen saturations, and can ultimately result in cardiac arrest (Figure 30.1).

Different institutions have published their experiences with anesthesia for CMR imaging and have found that the risk of adverse events is quite low [61,62]. However, Stockton et al. reported a 28% incidence of adverse events, higher than that of the general pediatric population. It is important to recognize that practically all risks associated with MRI are related to the anesthetic. Single-ventricle patients are known to have increased risk of morbidity and mortality associated with anesthesia, and this includes anesthesia for CMR [2]. Particular attention should be paid to fasting times and inadequate preoperative hydration. Both Stockton et al. and Brown et al. report major adverse events including death prior to the anesthetic (thought to be dehydration-related), intraoperative cardiac arrest, and shunt thrombosis in this population. These adverse events led to a modification to the CMR protocol to include a preadmission for intravenous fluids and possible heparin administration prior to the study [7,8]. At our institution, we have a low threshold to admit these patients to the hospital after the scan for continuation of intravenous hydration as needed and for observation. Inadequate post-anesthetic oral intake and anesthesia-related physiologic alterations, including possible hypotension and reduced shunt flow, can result in significant consequences. Proper multidisciplinary planning, an experienced anesthesiologist, and vigilant peri-anesthetic care can help to minimize this risk.

Because of the high-risk nature of some CMR studies, appropriate planning for resuscitation and rescue should be in place. Any question about the stability of the patient during the MRI should necessitate stopping the scan and an evaluation of the patient, with a low threshold to remove the patient from the scanner room into an adjacent resuscitation area where ferromagnetic equipment does not pose a safety risk. Many congenital cardiac centers now have MRI incorporated into their catheterization laboratory suites, where rapid imaging after catheter interventions is possible. These scanners double as the CMR diagnostic scanners and have the added advantage of closer proximity to help and expertise to rescue the patient from a critical event.

Until recent years, the presence of a cardiac pacemaker was essentially an absolute contraindication to MRI scanning. However, there are now a number of MRI-compatible pacemaker systems that have been tested in adult patients and which are generally deemed to be safe. It is likely that these systems will be implanted in pediatric patients in the future. The risk benefit of MRI in this situation must be completely evaluated, and alternative means to obtain the imaging data should be sought. A protocol for the device, and the presence of experts in managing the devices during the MRI scan are essential if an MRI-compatible pacemaker procedure is planned [63].

**KEY POINTS: MRI AND CT**

- Risk associated with imaging is almost entirely anesthesia-related.
- Airway monitoring is critical; hypercarbia and hypoxemia can lead to cardiac arrest in high-risk patients, especially those with pulmonary hypertension.
- High-risk patients may require preoperative admission and hydration and/or postoperative admission and monitoring for imaging procedures requiring anesthesia.

**Postoperative considerations**

**Intensive care unit vs. general inpatient unit**

Inpatient postoperative recovery may take place in an intensive care setting or on a general inpatient unit. The
decision about the postoperative setting should take a number of factors into consideration, including the cardiac diagnosis, the complexity of surgery, and potential postoperative difficulties. The decision to leave the trachea intubated at the end of the case necessitates an ICU admission.

The shunted single-ventricle circulation is fragile, and the risks and benefits of extubation must be weighed carefully. An extubated patient may develop apnea, hyperventilation, hypoxemia, hypercarbia, acidosis, and/or poor pain control; this may be catastrophic in a shunted single ventricle. In a series of five patients with HLHS after stage I palliation undergoing laparoscopic Nissen fundoplication, four were left intubated at the end of the operation. All were transferred to the ICU for recovery, and the remaining four patients were extubated on postoperative day 1. All had good outcomes [43].

Watkins et al. studied perioperative outcomes of 36 patients with HLHS after stage I palliation undergoing fundoplication and gastrostomy. Most patients were extubated in the OR and recovered on an in-patient unit. A substantial number of these patients developed cardiorespiratory instability postoperatively, and an escalation in care was required. During the study period, due to unplanned ICU admissions in this population, a policy was made that all patients with HLHS after stage I palliation should recover in an ICU after a general anesthetic [64].

In most other patients with CHD, recovery on a general inpatient unit is appropriate. However, patients should be monitored closely for respiratory difficulties, hemodynamic instability, desaturation, or arrhythmia, all of which can be poorly tolerated in the patient with CHD.

**Home discharge criteria**

It is possible to perform outpatient procedures on patients with CHD, but considerations should include the cardiac disease and stability of physiology, the type of procedure, and potential perioperative complications. Christensen et al. reported data on the anesthetic management and outcome in patients with surgically corrected dextro-transposition of the great arteries undergoing non-cardiac surgery [65]. In this series of 50 procedures, 71% of patients who had undergone arterial switch operation (corrective repair) and 60% of patients who had undergone atrial switch operation (physiologic repair), were discharged home on the day of the procedure.

It must be recognized, however, that mild complications of anesthesia or surgery, including dehydration due to nausea and vomiting, poor intake of fluids by mouth, or bleeding, can result in serious morbidity for intravascular volume-sensitive patients with CHD [9]. In addition, as stated earlier, the perioperative risk of patients with pulmonary hypertension extends into the post-anesthesia period [32]. These patients should not be discharged home on the day of surgery.

**KEY POINTS: POSTOPERATIVE CONSIDERATIONS**

- High-risk patients, such as patients with HLHS after the Norwood procedure, are commonly cared for in the ICU after a procedure due to their fragile circulation.
- Well-compensated patients with CHD can be discharged home on the day of surgery.
- Patients with pulmonary hypertension should be observed carefully after anesthesia and surgery.

**Selected references**

A full reference list for this chapter is available at: http://www.wiley.com/go/andropoulos/congenitalheart

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CHAPTER 31
Cardiac Intensive Care

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Introduction

The cardiac intensive care unit (CICU) serves as the primary destination for critically ill children with congenital and acquired heart disease. It provides an expert model of care by bringing the broad range of specific expertise to the bedside of such patients. Ideally, this allows the cardiac intensivist to engage in dynamic decision-making that involves anesthesiologists, cardiac surgeons, interventionalists, imaging specialists, electrophysiologists, and heart failure specialists serving to impact the quality of care delivery.

In contrast to general intensive care, the vast majority of CICU admissions are planned. With preoperative and pre-catheterization review and fetal echocardiography, it is possible and necessary to plan most admissions and their potential need for CICU resources.

At SickKids in Toronto we serve as the population referral center for congenital heart disease (CHD). As such our CICU and surgical population reflect the incidence of disease in our multicultural catchment area as opposed to center-specific referral bias. SickKids’ CICU admissions based on age and source are shown in Figures 31.1 and 31.2.

Pathophysiology of specific congenital cardiac defects and implications

A thorough understanding of the pathophysiology of congenital cardiac defects is essential when managing these patients in the CICU. This will influence not only pre-operative management strategy for stabilization and/or resuscitation prior to surgery, but also preparations for

the impact of pre-existing cyanosis, pressure, and volume overload on myocardial performance and recovery after surgery. Further, if there are hemodynamically significant residual intracardiac lesions after surgery, the accompanying alterations in pulmonary blood flow, systemic perfusion, and ventricular compliance may significantly affect recovery in the CICU.

**Intercirculatory mixing, complete mixing, and streaming**

Confusing terminologies are often used interchangeably to describe common pre- and postoperative physiologies. It is important for the care provider to understand the essential elements of the circulation in order to react appropriately to perturbations.
Intercirculatory mixing lesions

Patients with dextro-transposition of the great arteries (D-TGA) have parallel circulations: the deoxygenated systemic venous blood returns to the right ventricle (RV) and is ejected through the aorta. Oxygenated pulmonary venous blood is returned to the left ventricle (LV) and is ejected to the pulmonary artery (Figure 31.3). Although the figure depicts simple transposition anatomy, transposition physiology can occur with other anatomic arrangements such as Taussig–Bing type double outlet RV. Transposition physiology occurs when the pulmonary artery oxygen saturation is greater than the aortic oxygen saturation. Such a circulation is not compatible with survival over time unless there is adequate intercirculatory mixing that allows the deoxygenated systemic venous blood into the pulmonary circulation (PA), as well as the oxygenated pulmonary venous blood into the systemic circulation (aorta) [1]. Although 25–50% of patients with D-TGA have a ventricular septal defect (VSD), the presence of such does not guarantee adequate intercirculatory mixing. Newborns, regardless of whether they are diagnosed antenatally or postnatally, can present with profound cyanosis in the absence of respiratory distress. Such patients are transported to the CICU after commencing intravenous (IV) prostaglandin E₁ (PGE₁) to maintain a patent ductus arteriosus (PDA). After confirmation of the diagnosis of D-TGA with a restrictive or intact atrial septum, a balloon atrial septostomy (BAS) can be performed at the bedside or in the cardiac catheterization laboratory to allow optimal intercirculatory mixing and systemic oxygen delivery. If the atrial communication is restrictive, provision of usual therapies to improve pulmonary blood flow (supplemental oxygen, inhaled nitric oxide) are often detrimental, as these therapies can lead to left atrial hypertension and further impairment of atrial level mixing. Once an adequate atrial septal defect (ASD) is created, systemic oxygen delivery improves. Subsequently, patients can have the PGE₁ infusion discontinued and quickly wean and extubate to await an elective corrective operation within 7–10 days. Some patients with D-TGA may remain hypoxemic, despite creation of an unrestricted atrial communication; such patients often are dependent on PGE₁ infusion to maintain systemic saturations > 65%. The failure for adequate mixing at the atrial level may reflect differences in ventricular function, filling and ventricular end-diastolic pressures, but may also be secondary to a streaming effect. There may also be an element of rebound pulmonary hypertension reducing the volume of pulmonary blood flow without affecting the amount of intercirculatory mixing. Some investigators have suggested a protracted weaning protocol for PGE₁ to mitigate this effect [2]. See Chapter 24 for further discussion of TGA.

Complete mixing lesions

These represent a variety of anatomic entities that have a common chamber where pulmonary and systemic venous return completely mix before exiting. The common conventional terminology is single-ventricle physiology, namely, a physiology where the pulmonary artery saturation and aortic saturation are equal. These lesions can have either ductal-dependent pulmonary blood flow (tricuspid atresia, pulmonary atresia with intact ventricular septum) or ductal-dependent systemic blood flow (hypoplastic left heart syndrome [HLHS], double inlet LV). Although the majority of these lesions will require a palliative single-ventricle strategy, some patients with single-ventricle physiology have two anatomically adequate ventricles allowing for an initial septation procedure (truncus arteriosus, tetralogy of Fallot [TOF] with pulmonary atresia). This is important when considering the systemic oxygen saturation (SaO₂) targets in managing these patients. The traditional SaO₂ targets of 75–85% are important when trying to balance pulmonary blood flow (Qp) and systemic blood flow (Qs) in a pre- or postoperative patient with limited combined ventricular output, i.e., those patients with one anatomic pumping chamber. When combined ventricular output is not a limiting factor (preoperative patients with tricuspid atresia, HLHS, truncus arteriosus), it is important to recognize that strict management of Qp/Qs balance is unnecessary in the absence of respiratory embarrassment or signs of inadequate systemic oxygen delivery (DO₂). See Chapter 25 for further discussion of single-ventricle lesions.
Streaming

Streaming is the phenomenon where systemic venous blood (or pulmonary venous blood) can pass through to the systemic circulation (or pulmonary circulation) due to specific anatomic abnormalities such as a common atrium or absence of a common arterial septum. This streamed blood may or may not be completely mixed before it reaches the arterial outlet. If it is incompletely mixed, the physiology is likely to be that of transposition (\(P_{\text{A sat}} > P_{\text{O sat}}\)), whereas streaming that is completely mixed has single-ventricle physiology (\(P_{\text{A sat}} = P_{\text{O sat}}\)).

Shunts

Shunting between the pulmonary and systemic circulations can be intracardiac (across an ASD or VSD) or extracardiac (across a PDA, aortopulmonary window, decompressing veno-venous collaterals or aortopulmonary collateral). Depending on the size of the communication and the differential pressures and resistances between the pulmonary and systemic circulations, patients may have decreased or increased pulmonary blood flow and may be either cyanotic or acyanotic, respectively.

Increased pulmonary blood flow

Shunts that increase pulmonary blood flow may occur between the atria, ventricles, or great arteries, and they can be simple or complex. The degree of restriction across these shunts also affects their potential clinical significance.

Simple shunt

The amount of flow across a “simple” left-to-right shunt depends on the size of the defect and the balance between pulmonary vascular resistance (PVR) and systemic vascular resistance (SVR). It is important to understand that this is a physiologic term and has no direct relationship to specific diagnoses (Table 31.1). Therefore patients who have a simple shunt may have:

- A normal \(\text{SaO}_2\) with two ventricles, such as a large VSD, complete atrioventricular canal (CAVC), and large PDA
- A normal \(\text{SaO}_2\) with a single ventricular outflow trunk and two ventricles (truncus arteriosus)
- A “low” \(\text{SaO}_2\) (90–95%) and two ventricles (D-TGA with large VSD)
- A “low” \(\text{SaO}_2\) (85–95%) and single ventricle (tricuspid atresia or following Blalock–Taussig–Thomas shunt [BTT] such as in a Norwood procedure).

If the simple shunt is “unrestrictive,” the physiologic consequence for all these diagnoses will be the same, i.e., excessive pulmonary flow and volume overload to the ventricle receiving the excessive pulmonary venous blood flow. The degree of shunt will be determined not by the size of the defect, but rather by the relationship between SVR and PVR [3,4]. The clinical manifestation will also be the same, namely congestive heart failure (CHF) and pulmonary hypertension, although some patients will be cyanotic and others acyanotic, depending on the degree of intracardiac mixing.

On the other hand, for a simple “restrictive” shunt, when the orifice or size of the shunt is small, the size of the communication is the limiting factor determining the increase in pulmonary blood flow; relative SVR and PVR have little or no impact in this situation. In this circumstance, there is minimal overload to the ventricle receiving pulmonary venous flow, and the pulmonary circulation is protected from excess pressure and flow. As a result, patients may be relatively asymptomatic and present at an older age with non-specific symptoms such as recurrent respiratory infections or failure to thrive.

Complex shunt

In the presence of additional pulmonary or systemic outflow obstruction, the ratio of pulmonary to systemic blood flow (Qp/Qs) is determined by the size of the orifice, the outflow gradient, as well as SVR and PVR. The obstruction may be fixed (valvular aortic or pulmonary stenosis) or dynamic (some forms of TOF).

Clinical consequences of increased pulmonary to systemic blood flow ratio

If the increase in pulmonary blood flow and pressure persist over months to years, structural changes occur within the pulmonary vasculature until eventually PVR becomes irreversibly elevated [3–5]. The time course for developing this pathology, termed pulmonary vascular obstructive disease, depends in part on the amount and duration of shunting. Changes may be evident by 4–6 months of age in some lesions (e.g., truncus arteriosus). The progression is much more rapid when the volume and pressure overload

### Table 31.1 Simple shunts: defects or surgical procedures contributing to an increased pulmonary blood flow/systemic blood flow (Qp/Qs)

<table>
<thead>
<tr>
<th></th>
<th>Acyanotic</th>
<th>Cyanotic</th>
</tr>
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<tbody>
<tr>
<td>Two ventricles</td>
<td>ASD</td>
<td>D-TGA/VSD</td>
</tr>
<tr>
<td></td>
<td>VSD</td>
<td>PA/VSD</td>
</tr>
<tr>
<td></td>
<td>CAVC</td>
<td></td>
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<tr>
<td></td>
<td>DORV</td>
<td></td>
</tr>
<tr>
<td>Single ventricle</td>
<td>TA ± TGA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HLHS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DORV/MA</td>
<td></td>
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<td></td>
<td>Norwood procedure</td>
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<tr>
<td></td>
<td>BT shunt</td>
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<tr>
<td></td>
<td>PA/MAPCA</td>
<td></td>
</tr>
<tr>
<td>AP connection</td>
<td>PDA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Truncus arteriosus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AP window</td>
<td></td>
</tr>
</tbody>
</table>

ASD, atrial septal defect; VSD, ventricular septal defect; CAVC, complete atrioventricular canal; DORV, double outlet right ventricle; D-TGA, dextro-transposition of the great arteries; PA, pulmonary atresia; TA, tricuspid atresia; MA, mitral atresia; HLHS, hypoplastic left heart syndrome; BT, Blalock–Taussig; PDA, patent ductus arteriosus; MAPCA, major aortopulmonary collateral artery; AP, aortopulmonary.
to the pulmonary circulation are increased, such as with a large VSD or CAVC defect. When pulmonary blood flow is increased in the absence of pressure overload, such as in simple secundum ASD, pulmonary vascular obstructive disease develops much more slowly if at all.

As PVR decreases in the first weeks to months after birth, and the hematocrit falls to its lowest physiologic value, the increased left-to-right shunt, and therefore the volume load on the systemic ventricle, can lead to CHF.

A typical pressure–volume loop for a volume-loaded ventricle is shown in Figure 31.4. The end-diastolic volume is increased and the end-diastolic pressure–volume line is displaced to the right, indicating reduced contractility. The time course over which irreversible ventricular dysfunction develops is variable, but if surgical/catheter intervention to correct the volume overload is undertaken within the first 2 years of life, residual dysfunction is uncommon [6]. The volume load on the systemic ventricle and increased end-diastolic pressure–volume line is displaced to the right, indicating reduced contractility. The time course over which irreversible ventricular dysfunction develops is variable, but if surgical/catheter intervention to correct the volume overload is undertaken within the first 2 years of life, residual dysfunction is uncommon [6].

The lung fields are usually congested as well as hyperinflated. Ventilation/perfusion mismatch contributes to an increased alveolar-to-systemic arterial (A–aO₂) gradient and dead space ventilation [9]. Minute ventilation is therefore increased, primarily by an increase in respiratory rate. Pulmonary artery and left atrial enlargement may compress main-stem bronchi, causing lobar collapse.

It is important to appreciate that such clinical scenarios can be present even after surgery in patients who have significant residual intracardiac shunts that cause an increase in Qp/Qs. It may be manifest during the early postoperative course as a low cardiac output state (LCOS; see later) or become apparent some days after surgery with an inability to wean from mechanical ventilation or a persistent requirement for vasoactive support.

**Decreased pulmonary blood flow**

Reductions to pulmonary blood flow from structural heart disease are ultimately related to intracardiac right-to-left shunting. The basis for this may be pulmonary outflow obstruction (supravalvular, valvular, subvalvular or a combination thereof) or subpulmonary ventricle inflow obstruction (tricuspid stenosis or atresia). In patients with non-cardiac diseases, such as persistent pulmonary hypertension of the newborn, persistent elevations in PVR result in intracardiac (or ductal) right-to-left shunting.

Pulmonary mechanics and lung volumes are generally normal in patients with reduced pulmonary blood flow. Dead space ventilation is increased, although minute ventilation is only slightly increased to maintain normocapnia. The lung fields appear oligemic on chest radiograph. Patients with TOF and absent pulmonary valve syndrome can have massively dilated branch pulmonary arteries that compress on large and small airways. These patients have significant gas-trapping and expiratory-flow limitations,
Inappropriately low set oxygen extraction:

Systolic dysfunction of a hypertrophied ventricle may arise from a right-to-left shunt (across a patent foramen ovale [PFO] or ASD), hepatomegaly, pleural effusions, and possibly ascites.

Diastolic dysfunction is usually manifest as a poorly compliant or stiff ventricle that often contracts well, but is unable to relax and fill effectively during diastole.

Potential causes of low SaO₂ include:

1. Pulmonary venous desaturation (normal 95–99% in ambient air), indicating an intrapulmonary shunt such as alveolar edema/consolidation or pleural effusion
2. A reduction in effective pulmonary blood flow, such as from pulmonary outflow obstruction, increased PVR, intracardiac right-to-left shunt or decompressing venovenous collaterals (from a high-pressure superior vena cava in a Glenn circulation to the inferior vena cava)
3. A reduction in arterial oxygen content (CaO₂), principally in patients who have mixing of systemic and pulmonary venous blood at the atrial level. The reduction in CaO₂ may be due to low mixed venous oxygen level (such as reduced oxygen delivery due to impaired cardiac output [CO] or increased oxygen extraction) or a low oxygen-carrying capacity (reduced hematocrit).

### Outflow obstruction

Severe left or right ventricular outflow obstruction in the newborn may be associated with ventricular hypertrophy and vessel hypoplasia distal to the level of obstruction. The increased pressure load may cause ventricular failure, with mixing or shunting at the ASD and/or VSD level to maintain systemic CO if there is complete outflow obstruction. A typical pressure–volume loop from a chronic pressure load on the ventricle is shown in Figure 31.4. The end-diastolic pressure is elevated and the end-systolic pressure–volume line is shifted to the left, reflecting increased contractility (in the compensated state). Maintenance of preload, stability in afterload, and normal sinus rhythm are important to prevent a fall in CO or coronary hyperperfusion. As the time course to develop significant ventricular dysfunction is longer in patients with chronic pressure overload compared with chronic volume overload, symptoms of CHF are uncommon, unless obstruction is severe or prolonged.

In the immediate postoperative period, it is important to evaluate both systolic and diastolic ventricular function in a previously obstructed but still hypertrophied ventricle, as follows:

1. A hyperdynamic state may be present following LV outflow reconstruction. This will be manifest by systemic hypertension and should be treated promptly to reduce myocardial work and protect surgical suture lines, especially those in the aorta.
2. Systolic dysfunction of a hypertrophied ventricle may be apparent early after cardiac surgery secondary to myocardial ischemia and ventricular dysrhythmias. Ischemia may occur particularly if there has been a long aortic cross-clamp time, or if there is inadequate myocardial protection with cardioplegia solution or hypothermia. In the case of the RV, dysfunction may be related to a right ventriculotomy, direct injury to a coronary artery (running across the RV outflow tract), air embolism, or due to relatively poor protection with cardioplegia, hypothermia, or local cooling strategies.
3. Diastolic dysfunction is usually manifest as a poorly compliant or stiff ventricle that often contracts well, but is unable to relax and fill effectively during diastole. On the left side of the heart, this is usually manifest as left atrial hypertension with either pulmonary edema, atrial dysrhythmias, or pulmonary hypertension. On the right side of the heart, an increase in RV end-diastolic pressure is demonstrated by right atrial hypertension along with clinical signs such as atrial arrhythmias, lower SaO₂ from a right-to-left shunt (across a patent foramen ovale [PFO] or ASD), hepatomegaly, pleural effusions, and possibly ascites.

### Table 31.2 Factors to consider in a postoperative cardiac surgery patient with an arterial oxygen saturation lower than the anticipated range

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low FiO₂</td>
<td>Inappropriately low set oxygen concentration for delivery</td>
</tr>
<tr>
<td>Pulmonary vein desaturation</td>
<td>Failure of oxygen delivery device</td>
</tr>
<tr>
<td>Reducing pulmonary blood flow</td>
<td>Impaired diffusion</td>
</tr>
<tr>
<td>Low dissolved O₂ content</td>
<td>Alveolar process: edema, infection</td>
</tr>
<tr>
<td>Anatomic RV outflow obstruction</td>
<td>Restrictive process: effusion, atelectasis, pneumothorax</td>
</tr>
<tr>
<td>Anatomic pulmonary artery stenosis</td>
<td>Increased PVR</td>
</tr>
<tr>
<td>Ventricular level right-to-left shunt</td>
<td>RV hypertension</td>
</tr>
<tr>
<td>Pulmonary AVM</td>
<td>Restrictive RV physiology (low compliance)</td>
</tr>
<tr>
<td>PA-to-PV collateral vessel(s)</td>
<td>Severe tricuspid regurgitation</td>
</tr>
<tr>
<td>Large fenestration (modified Fontan operation)</td>
<td>Left atrial baffle leak</td>
</tr>
<tr>
<td>Intra-atrial baffle leak</td>
<td>Ventricular level right-to-left shunt</td>
</tr>
<tr>
<td>RV hypertension and residual VSD</td>
<td>Increased O₂ extraction: hypermetabolic state</td>
</tr>
<tr>
<td>Decrease O₂ delivery: low cardiac output state</td>
<td>Anemia</td>
</tr>
</tbody>
</table>

FiO₂, fractional inspired concentration of oxygen; RDS, respiratory distress syndrome; PA, pulmonary artery; AVM, arteriovenous malformation; PV, pulmonary vein; RV, right ventricle; PVR, pulmonary vascular resistance; VSD, ventricular septal defect; O₂, oxygen; SVO₂, single ventricle; TGA, transposition of the great arteries.

which is a frequent cause of their respiratory failure, necessitating newborn corrective repair.

### Target systemic oxygen saturation level

The postoperative target SaO₂ level is important to establish, as it will guide assessment and therapeutic intervention (Table 31.2). Potential causes of low SaO₂ include:

- Pulmonary venous desaturation (normal 95–99% in ambient air), indicating an intrapulmonary shunt such as alveolar edema/consolidation or pleural effusion
- A reduction in effective pulmonary blood flow, such as from pulmonary outflow obstruction, increased PVR, intracardiac right-to-left shunt or decompressing venovenous collaterals (from a high-pressure superio
  r vena cava in a Glenn circulation to the inferior vena cava)
- A reduction in arterial oxygen content (CaO₂), principally in patients who have mixing of systemic and pulmonary venous blood at the atrial level. The reduction in CaO₂ may be due to low mixed venous oxygen level (such as reduced oxygen delivery due to impaired cardiac output [CO] or increased oxygen extraction) or a low oxygen-carrying capacity (reduced hematocrit).
Airway and ventilation management

In all the above examples of mixing, shunting, and outflow obstruction, the mode and method of mechanical ventilation may have a substantial impact on hemodynamics and systemic perfusion. Particularly for neonates and infants, cardiorespiratory interactions are essential to recognize during postoperative management. While changes in the partial pressure of oxygen (PaO₂), partial pressure of carbon dioxide (PaCO₂), and pH are well recognized to significantly affect PVR, the mean airway pressure and changes in lung volume during positive pressure ventilation (PPV) will also affect PVR, preload, and ventricular afterload. In addition to evaluating the adequacy of mechanical ventilation settings by arterial blood gas and chest radiography, it is important that ventilator settings be continually evaluated and adjusted according to hemodynamic response.

Airway management

Intubation of the trachea in an awake neonate or young infant with CHD may elicit major undesirable hemodynamic and metabolic responses, and therefore appropriate anesthetic techniques are desirable to secure the airway in most circumstances.

The narrowest part of the airway before puberty is below the vocal cords at the level of the cricoid cartilage. Before the introduction of low-pressure, low-profile balloon cuffs on endotracheal tubes, the use of uncuffed endotracheal tubes had been generally recommended. While a leak around the endotracheal tube at an inflation pressure of approximately 20 cmH₂O is desirable, a significant air leak may have a detrimental effect on mechanical ventilation and delivery of a consistent ventilation pattern. Examples include patients with extensive chest and abdominal wall edema following cardiopulmonary bypass (CPB) and patients with labile PVR and increased Qp/Qs. If a significant air leak exists around the endotracheal tube, lung volume, and in particular functional residual capacity (FRC) will not be maintained and fluctuations in gas exchange can occur. During the ventilator weaning process, a significant leak will also increase the work of breathing for some neonates and infants. In these situations, it is therefore preferable to change the endotracheal tube to a larger size or to use a cuffed endotracheal tube. In contrast, a smaller than usual endotracheal tube may be necessary in certain situations. This is particularly the case in patients with other congenital defects such as Down syndrome (trisomy 21). Tracheal stenosis may also occur in association with some congenital cardiac defects such as a pulmonary artery sling. Extrinsic compression of the bronchi may occur by the pulmonary artery or a dilated left atrium. This may be suspected by persistent hyperinflation or lobar atelectasis on chest radiograph.

Mechanical ventilation

Altered lung mechanics and ventilation/perfusion abnormalities are common problems in the immediate postoperative period [9]. Patients who have a Qp/Qs > 2:1 may have cardiomegaly and congested lung fields on chest radiograph. Patients who have an elevated left atrial pressure from some form of outflow tract obstruction to the LV may demonstrate signs of pulmonary venous hypertension and pulmonary edema. Additional considerations include the surgical incision and lung retraction, increased lung water following CPB, possible pulmonary reperfusion injury, surfactant depletion in neonates, and restrictive defects from atelectasis and pleural effusions.

In general, patients with known, limited physiologic reserve should not be weaned from mechanical ventilation until hemodynamically stable and any problems contributing to an increase in intrapulmonary shunt and altered respiratory mechanics have improved.

Cardiorespiratory interactions

Cardiorespiratory interactions vary significantly between patients, and it is not possible to provide specific ventilation strategies or protocols that are appropriate for all patients. Rather, the mode of ventilation must be matched to the hemodynamic status of each patient to achieve an adequate CO and gas exchange. The influence of PPV on preload and afterload is shown in Table 31.3. Frequent modifications to the mode and pattern of ventilation may be necessary during recovery after surgery with attention to changes in lung volume, compliance, and airway pressure.

Influence of lung volume

Changes in lung volume have a major effect on PVR, which is lowest at FRC, as both atelectasis and hyperinflation may result in a significant increase in PVR, as shown in Figure 31.5 [10–12]. At low tidal volumes, alveolar collapse occurs because of reduced interstitial traction on alveolar septae. In addition, radial traction...
Table 31.3 The effect of a positive pressure mechanical breath on afterload and preload to the pulmonary and systemic ventricles

<table>
<thead>
<tr>
<th>Afterload</th>
<th>Preload</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary ventricle</td>
<td></td>
</tr>
<tr>
<td>Elevated</td>
<td>Reduced</td>
</tr>
<tr>
<td>Effect: ↑ RVEDp</td>
<td>Effect: ↓ RVEDV</td>
</tr>
<tr>
<td>↓ RVp</td>
<td>↓ RAp</td>
</tr>
<tr>
<td>↓ Antegrade PBF</td>
<td></td>
</tr>
<tr>
<td>Systemic ventricle</td>
<td>Reduced</td>
</tr>
<tr>
<td>Effect: ↓ LVEDp</td>
<td>Effect: ↓ LVEDV</td>
</tr>
<tr>
<td>↓ LAp</td>
<td>↓ LAp</td>
</tr>
<tr>
<td>↓ Pulmonary edema</td>
<td>Hypotension</td>
</tr>
</tbody>
</table>

RVEDp, right ventricle end-diastolic pressure; RVp, right ventricle pressure; RVEDV, right ventricle end-diastolic volume; PBF, pulmonary blood flow; PR, pulmonary regurgitation; TR, tricuspid regurgitation; LVEDp, left ventricle end-diastolic pressure; LVEDV, left ventricle end-diastolic volume; LAp, left atrial pressure; RAp, right atrial pressure.

Figure 31.5 Lung volume impacts pulmonary vascular resistance (PVR). In the diagram, there is a marked decrease in PVR when increasing lung volume from residual volume (RV) to functional residual capacity (FRC). This is mainly a function of opening alveoli strutting open extra-alveolar vessels (drop in extra-alveolar resistance; dotted line). Further increases in lung volume from FRC to total lung capacity (TLC) cause increases in PVR. This is mainly due to compression of intra-alveolar vessels by air-trapping (alveolar component; dashed line). Total PVR is minimized at FRC (solid line).

on extra-alveolar vessels such as the branch pulmonary arteries is reduced, therefore reducing the cross-sectional diameter. Conversely, hyperinflation of the lung may cause stretching of the alveolar septae and compression of alveolar vessels.

An increase in PVR increases the afterload or wall stress on the RV, compromising RV function and contributing to decreased LV compliance secondary to interventricular septal shift (from right to left). In addition to low CO, signs of RV dysfunction, including tachycardia, tricuspid regurgitation, hepatomegaly, ascites, and pleural effusions, may be observed.

Influence of intrathoracic pressure
An increase in mean intrathoracic pressure during PPV decreases preload to both pulmonary and systemic ventricles, but has opposite effects on afterload of each ventricle [13–15].

Right ventricle
The increase in pressure in the right atrium and reduction in RV preload that occurs with PPV may reduce CO. Normally, RV diastolic compliance is high and the pulmonary circulation is able to accommodate changes in flow without a large change in pressure. An increase in mean intrathoracic pressure increases the afterload on the RV from direct compression of extra-alveolar and alveolar pulmonary vessels. This has a number of clinical consequences (Table 31.3). An increase in afterload causes an increase in RV end-diastolic pressure and myocardial work, which may lead to ischemia in a patient with limited coronary perfusion. An example of the increase in RV pressure during a positive pressure breath is demonstrated in Figure 31.6. The increase in afterload on the RV will also reduce anterograde pulmonary blood flow and therefore preload to the systemic ventricle. If there is pulmonary or tricuspid valve incompetence, the amount of regurgitant flow across these valves will also increase during PPV from the increase in RV afterload.

Patients with normal RV compliance and without residual volume load or pressure load on the ventricle following surgery usually show little change in RV function from the alteration in preload and afterload that occurs with PPV. However, these effects can be magnified in patients with RV hypertrophy and those with restrictive RV physiology following congenital heart surgery; in particular, neonates who have required a right ventriculotomy for repair of TOF with pulmonary atresia or truncus arteriosus and patients with concentric RV hypertrophy are at risk. While systolic RV function may be preserved, the ventricles have diastolic dysfunction with increased RV end-diastolic pressure and impaired RV filling.
It is important to emphasize the potentially deleterious effects of mechanical ventilation on RV function. The aim should be to ventilate with a mode that enables the lowest possible mean airway pressure, while maintaining adequate lung volume. A mode of mechanical ventilation that limits potential secondary injury to the lung is the ideal in any critical care setting. A low tidal volume strategy (4–6 mL/kg) is recommended in patients with lung disease, such as pneumonia, adult respiratory distress syndrome, and lung disease of prematurity. This is achieved using a low peak inspiratory pressure, short inspiratory time, increased intermittent mandatory ventilation (IMV) rate, and higher levels of positive end-expiratory pressure (PEEP). However, this strategy is also associated with a higher mean intrathoracic pressure and afterload on the RV, and a longer expiratory time which reduces antegrade pulmonary blood flow. Therefore, this mode may be detrimental in patients with restrictive RV physiology where a strategy utilizing larger tidal volumes (10–12 mL/kg), lower rates (15–20 breaths/minute), larger peak inspiratory pressure-PEEP difference, and longer inspiratory times (0.8–0.9 seconds) may be preferential.

**Left ventricle**

Left ventricular preload is also affected by changes in lung volume. Pulmonary blood flow and therefore preload to the systemic ventricle may be reduced by an increase or decrease in lung volume secondary to alteration in radial traction on alveolar and extra-alveolar vessels.

The systemic arteries are under higher pressure and not exposed to radial traction effects during inflation or deflation of the lungs. Therefore, changes in lung volume will affect LV preload, but the effect on afterload is dependent on changes in intrathoracic pressure alone rather than changes in lung volume.

In contrast to the RV, a major effect of PPV on the LV is a reduction in afterload. Using the law of Laplace, wall stress is directly proportional to the transmural LV pressure and the radius of curvature of the LV, and inversely proportional to the thickness of the ventricle. The transmural pressure across the LV is the difference between the intracavity LV pressure and the surrounding intrathoracic pressure. Assuming a constant arterial pressure and ventricular dimension, an increase in intrathoracic pressure, as occurs during PPV, will reduce the transmural gradient and therefore wall stress on the LV (Figure 31.7). Therefore, PPV and PEEP can have significant beneficial effects in patients with LV failure (Table 31.3).

Patients with LV dysfunction and increased end-diastolic volume and pressure can have impaired pulmonary mechanics secondary to increased lung water, decreased lung compliance, and increased airway resistance. The work of breathing is increased and neonates can fatigue early because of limited respiratory reserve. A significant proportion of total body oxygen consumption is directed at the increased work of breathing (especially the diaphragm) in neonates and infants with LV dysfunction, contributing to poor feeding and failure to thrive. Therefore, PPV has an additional benefit in patients with significant volume overload and systemic ventricular dysfunction by reducing the work of breathing and oxygen demand.

Weaning from PPV may be difficult in patients with persistent systemic ventricular dysfunction. As spontaneous ventilation increases during the weaning process, swings in mean intrathoracic pressure may substantially alter afterload on the systemic ventricle. Once extubated, the sub-atmospheric intrapleural pressure means that the transmural pressure across the systemic ventricle is increased. This sudden increase in wall stress may contribute to an increase in end-diastolic pressure and volume, leading to pulmonary edema and a low output state. It may be difficult to determine which patients are likely to fail extubation because of ventricular failure; even a small amount of positive pressure, as used during continuous positive airway pressure (CPAP) or pressure support modes of ventilation, may be sufficient to reduce afterload and myocardial work. Inotropic agents, vasodilators, and diuretics should be continued throughout the weaning process and early after extubation to maintain stable ventricular function in these patients.

**Positive end-expiratory pressure**

The use of PEEP in patients with CHD has two important effects, those of recruiting FRC and O₂ reserve capacity, as well as redistributing lung water from alveolar septal regions to the more compliant perihilar regions. Gas exchange is improved and the work of breathing reduced. This is particularly important in patients with a volume load, ventricular dysfunction, and elevated end-diastolic volume. PEEP should, therefore, be used in all mechanically ventilated patients following congenital heart surgery. However, excessive levels of PEEP can be detrimental by increasing afterload on the RV. Usually 3–5 cmH₂O of PEEP will help to maintain FRC and redistribute lung water without causing hemodynamic compromise.

The use of PEEP in patients who have undergone a Fontan procedure or cavopulmonary anastomosis has also been debated. In this group of patients, pulmonary blood flow is non-pulsatile and depends on the pressure gradient between the superior vena cava and the pulmonary venous atrium. During PPV, pulmonary blood flow can be diminished, and during a Valsalva maneuver and at high levels of PEEP, retrograde pulmonary blood flow may be demonstrated by Doppler echocardiography. Nevertheless, the beneficial effects of PEEP to 5 cmH₂O as outlined above can be demonstrated following the Fontan procedure, and, at this level, it rarely contributes to a significant clinical decrease in effective pulmonary blood flow.

**Alternative modes of ventilation and respiratory support**

The use of high-frequency oscillatory ventilation (HFOV) has been beneficial in the management of hypoxemic
Transmural aortic pressure affects left ventricular afterload. By the law of Laplace, the transmural aortic pressure ($P_{TM}$) is affected by intrapleural pressure. During normal breathing (A), there is very little effect of the intrapleural pressure on $P_{TM}$ and thus left ventricular afterload.

Generation of pathologic degrees of negative intrapleural pressure (as with severe airway obstruction or decompensated heart failure) significantly increases left ventricular afterload (B). Provision of positive pressure ventilation (PPV) (C) or pharmacologic afterload reduction (D) can both independently reduce left ventricular afterload. ITP, intrathoracic pressure. Pressure units are mm Hg.

and hypercapneic respiratory failure where the goal is to optimize systemic oxygen delivery while minimizing lung injury. The mean airway pressure may be higher than when using conventional ventilation, but can be well tolerated hemodynamically, provided preload is maintained. There is no defined indication for HFOV, but it should be considered in the setting of ventilatory failure with a rising $PaCO_2$ and mean airway pressures $>14$ cmH$_2$O in neonates and $>16$ cmH$_2$O in older children using conventional ventilator modes. Recent data using propensity matching suggest that HFOV might reduce the length of ventilation after CHD surgery in neonates and infants [16].

Early extubation can be advantageous in patients with restrictive RV physiology or absent subpulmonary ventricle (cavopulmonary connection or Fontan procedure). When this cannot be immediately achieved due to other considerations (postoperative bleeding or need for airway protection), airway pressure release ventilation can be a mode of ventilation that optimizes pulmonary blood flow and allows comfortable spontaneous ventilation [17]. Although negative pressure ventilation using a cuirass ventilator has been shown to achieve these same goals, use outside a research protocol is generally impractical [18].

Non-invasive ventilation (NIV) using either mask CPAP, bi-level positive airway pressure or high-flow nasal cannula can be a helpful adjunct in patients who are tachypneic with an increased work of breathing, those requiring improved oxygenation through maintenance of FRC, and to potentially improve CO and ventricular function by reducing wall stress and afterload. Of course, NIV also avoids the attendant risk of endotracheal intubation, including escalating sedation requirements and ventilator-associated pneumonia and tracheitis [19].

High-flow nasal cannula with humidified oxygen at flow rates of between 3 and 10 L/min can be used to
help minimize work of breathing and caloric expenditure in patients weaned from mechanical ventilation and/or those awaiting surgery. Although the PEEP delivered through this mode is variable, this mode is a helpful adjunct, especially in small patients with resting lung volumes approaching closing capacity [20].

**Weaning from mechanical ventilation**

Weaning from mechanical ventilation is a dynamic process that requires continued re-evaluation. While most patients following uncomplicated congenital cardiac surgery will wean without difficulty, some patients with borderline cardiac function and residual defects may require prolonged mechanical ventilation and a slow weaning process. The method of weaning varies between patients. Most patients can be weaned using either a volume- or pressure-limited mode by simply decreasing the intermittent mandatory ventilation rate. Guided by physical examination, hemodynamic criteria, respiratory pattern, and arterial blood gas measurements, the mechanical ventilator rate is gradually reduced. Patients with limited hemodynamic and respiratory reserve may demonstrate tachypnea, diaphoresis, and shallow tidal volumes as they struggle to breathe spontaneously against the resistance of the endotracheal tube. The addition of pressure- or flow-triggered pressure or volume support breaths above PEEP at a level related to the size of the endotracheal tube is often beneficial in reducing the work of breathing.

A flow-triggered mode of pressure or volume support, with a back-up ventilator rate if the patient becomes apneic (assist-control mode), is particularly useful for neonates and infants who have required either prolonged ventilation following surgery or a residual volume or pressure load compromising ventricular function. Patients are often more comfortable weaning in this mode and have reduced work of breathing, and the level of pressure support is adjusted according to their gas exchange, respiratory rate, and tidal volume. Numerous factors contribute to the inability to wean from mechanical ventilation following congenital heart surgery (Box 31.1). As a general rule, however, residual defects following surgery causing either a volume or pressure load must be excluded first by echocardiography or cardiac catheterization.

**Restrictive defects**

Pulmonary edema, pleural effusions, and persistent atelectasis may delay weaning from mechanical ventilation. Residual chest and abdominal wall edema, ascites, and hepatomegaly limit chest wall compliance and diaphragmatic excursion. Chest tubes and peritoneal catheters may be necessary to drain pleural effusions and ascites, respectively.

If atelectasis persists, bronchoscopy is often useful to remove secretions and to diagnose extrinsic compression from enlarged pulmonary arteries, a dilated left atrium, or conduits. Patients rarely fail from mild mechanical or dynamic airway compression alone and often have contributory residual lesions [21].

Phrenic nerve injury can occur during cardiac surgery secondary to traction, thymic resection, thermal injury from electrocautery, or direct transection as a complication of extensive aortic arch and pulmonary hilar dissection. Diaphragmatic paresis (no motion) or paralysis (paradoxical motion) should be investigated in any patient who fails to wean and extubate [22]. Increased work of breathing, abnormal respiratory mechanics, increased PaCO₂, and/or an elevated hemidiaphragm on chest radiograph following extubation are all consistent with diaphragmatic dysfunction. Ultrasonography or fluoroscopy is useful for identifying abnormal diaphragmatic movement. It is vital that such investigations are performed off positive pressure support. Additional discussion of airway management, ventilation, and extubation strategies is presented in Chapters 19 and 20.

**Fluids and nutrition**

Fluid restriction and aggressive diuretic therapy can result in metabolic disturbances and limit nutritional intake. A hypochloremic, hypokalemic metabolic alkalosis with secondary respiratory acidosis is a common complication from high-dose loop-diuretic use and can delay the ventilator weaning process. Diuretic therapy should be continually re-evaluated based on fluid balance, daily weight (if possible), clinical examination, and

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**Box 31.1: Factors contributing to the inability to wean from mechanical ventilation after congenital heart surgery**

**Residual cardiac defects**
- Volume and/or pressure overload
- Myocardial dysfunction
- Arrhythmias

**Restrictive pulmonary defects**
- Pulmonary edema
- Pleural effusion
- Atelectasis
- Pneumothorax
- Chest wall edema
- Phrenic nerve injury
- Ascites
- Hepatomegaly

**Airway**
- Subglottic edema and/or stenosis
- Retained secretions
- Vocal cord injury
- Extrinsic bronchial compression
- Tracheobronchomalacia

**Metabolic**
- Inadequate nutrition
- Diuretic therapy
- Sepsis
- Stress response
measurement of electrolyte levels and blood urea nitrogen. Chloride and potassium supplementation are essential to correct the metabolic acidosis.

It is critical to maintain adequate nutrition, particularly as patients will have catabolic metabolism early following cardiac surgery and may have a limited reserve secondary to preoperative failure to thrive. Fluid restriction may limit parenteral nutrition, and enteral nutrition may be poorly tolerated from splanchnic hypoperfusion secondary to low CO or low diastolic pressure (e.g., with an aortopulmonary shunt).

**Analgesia and sedation**

Adequate analgesia and sedation are necessary to optimize synchronization with the ventilator and maintain hemodynamic stability. Depending on the age of the patient, the magnitude of the operation, residual defects, and the preoperative condition, there is potential for both escalation and prolongation of these requirements.

Appropriate analgesia can often be provided with a low-dose opioid infusion. Although escalation may seem necessary based on clinical concerns, in particular hypertension or tachycardia, these are often secondary to inadequate sedation rather than from pain. A benzodiazepine is useful in these circumstances. The appropriate drug must take into account the anticipated duration of mechanical ventilation and the need to rapidly titrate to drug effect. When early extubation is planned, short-acting, non-opioid drugs such as dexmedetomidine and ketorolac are useful [23]. Use of a propofol infusion is also helpful in selected patient groups where agitation during rapid weaning is a sign of intolerance to airway stimulation as opposed to failure to wean from other causes; propofol infusion is not approved for use in neonates and infants, and must be used with caution because of hemodynamic complications and risk for propofol infusion syndrome [24].

Over-sedation can impair the rapid weaning process because of somnolence, leading to hypoventilation, failure to trigger the ventilator, and inability to protect the airway. Termination of additional opioid or sedation therapy and evaluation of the clinical response is often all that is required in this scenario, accepting, however, that patients may be agitated with periods of hypertension or tachycardia. This should be approached as a rapid process, similar to emergence and extubation from anesthesia, rather than weaning from a prolonged period of mechanical ventilation.

For patients who have required mechanical ventilation for a longer period of time, and therefore received higher cumulative doses and a range of analgesic and sedative medicines, rapid weans from analgesics and sedatives can result in withdrawal symptoms. These symptoms can often be confused with pulmonary or cardiac reasons for failure to wean, as respiratory and hemodynamic symptoms may predominate. It is important to have a systematic analgesia/sedation weaning protocol that incorporates timing of weaning with objective withdrawal assessment and knowledge of pharmacokinetics [25].

**Sepsis**

Sepsis is a particular risk following cardiac surgery for a number of reasons, including the immunomodulating effects of CPB, risk factors such as an open sternum, the use of invasive catheters for monitoring, and liberal use of broad-spectrum antibiotics. Sepsis can be a cause of failure to wean from mechanical ventilation because of the systemic effects, increased work of breathing, and the imbalance between oxygen demand and delivery, and should be actively pursued. Frequent culture surveillance is needed as well as monitoring biomarkers such as C-reactive protein and leukocytosis. Healthcare-acquired infections are preventable, and the use of established catheter insertion, access, and maintenance bundles is essential [26]. Ideally, percutaneous invasive catheters should be removed as soon as possible after surgery; if longer-term vascular access is anticipated, the placement of a transthoracic atrial catheter at the time of surgery or a peripheral inserted central catheter should be considered.

**Airway**

Bronchospasm can complicate mechanical ventilation and the weaning process. While this may reflect intrinsic airway disease, bronchospasm can also result from increased airway secretions and extrinsic airway compression. Treatment with inhaled or systemic bronchodilators may be beneficial, although they should be used with caution because of their chronotropic and tachyarrhythmic potential.

The sudden onset of bronchospasm with increased peak inspiratory pressure and difficulty with hand ventilation should raise the immediate concern for acute endotracheal tube obstruction or pneumothorax. Bronchospasm in patients with labile PVR may reflect acute pulmonary hypertension, and treatment is directed at maneuvers to lower pulmonary artery pressure and improve CO.

Post-extubation stridor may be due to mucosal swelling of the large airway, and treatment with dexamethasone before extubation can be beneficial to reduce edema in patients who have required prolonged mechanical ventilation. Stridor following extubation can initially be treated with nebulized epinephrine, which promotes vasoconstriction and decreases airway hyperemia and edema. If reintubation is necessary, a smaller endotracheal tube should be used. Vocal cord dysfunction should also be considered, particularly as surgery around the ductus arteriosus and left pulmonary artery may injure the recurrent laryngeal nerve; flexible laryngoscopy is useful to evaluate vocal cord function, particularly if the patient has a poor cough, weak cry, and/or stridor.

The ability to clear secretions and the potential for nosocomial infection are additional concerns in patients who have been ventilated for an extended period of
time. Inability to clear secretions because of sedation, bulbar and vocal cord dysfunction, ineffective cough following prolonged intubation, and poor nutritional state with muscle fatigue will result in atelectasis and respiratory failure. Frequent chest physiotherapy, mask CPAP, and nasopharyngeal suction are beneficial, provided that patients are hemodynamically stable with adequate gas exchange. In tachypneic patients, the use of nasopharyngeal CPAP and/or a high-flow nasal cannula can be beneficial by reducing the work of breathing; however, these patients have limited reserve, and frequent reassessment is essential.

**KEY POINTS: AIRWAY AND VENTILATION IN CHD**

- The lowest PVR is achieved by ventilating around FRC.
- PPV will reduce RV output by reducing preload and increasing RV afterload. This may be clinically deleterious in patients without a subpulmonary pumping chamber or with a restrictive RV.
- PPV will reduce work of breathing, LV afterload, and myocardial work.
- Failure of ventilator weaning can be due to a residual cardiac lesion or be non-cardiac in nature.

**Myocardial dysfunction and hemodynamic monitoring**

**Assessment of CO**

The accurate assessment of the postoperative patient’s CO should be a focus of management in the CICU. Establishing an adequate CO is important, because low CO is associated with longer duration of mechanical ventilatory support and CICU and hospital length of stay, all of which can increase the risk of morbidity and/or mortality [27, 28]. Data from physical examination, routine laboratory testing, bedside hemodynamic monitoring, echocardiography, and occasionally bedside CO determination are typically sufficient to manage patients optimally. If patients are not progressing as expected and low CO persists, a systematic evaluation for residual lesions and/or rhythm disturbances should occur. The former typically occurs through echocardiography, cardiac catheterization, or computed tomographic (CT) angiography.

The systemic CO is defined as the product of ventricular stroke volume (in L/beat) multiplied by heart rate (in beats/min). The ventricular stroke volume is determined chiefly by three factors: afterload (the resistance to ventricular emptying), preload, and myocardial contractility. CO is usually indexed to body surface area (BSA, in m²) because it is a function of body mass. Thus, CO/BSA is designated cardiac index (CI) (in L/min/m²). The CI varies inversely with age so that normal values in children at rest are 4.0–5.0 L/min/m², whereas the normal resting CI at age 70 years is 2.5 L/min/m² [29, 30].

Postoperative patients with low CO can present with a variety of abnormalities on physical examination, bedside monitoring, and laboratory assessment. These manifestations of low CO are listed in Box 31.2. Clinical signs on examination include cool extremities and diminished peripheral perfusion, tachycardia, hypotension, oliguria,

**Box 31.2: Manifestations of low cardiac output**

**Physical examination**

- Mental status: lethargy or irritability
- Vital signs:
  - Core hyperthermia (often associated with peripheral vasoconstriction)
  - Tachycardia or bradycardia
  - Tachypnea
  - Hypotension (for age and weight)
  - Narrow pulse pressure
- Peripheral perfusion:
  - Pale or mottled skin color and cool skin temperature
  - Prolonged (>3 seconds) distal extremity capillary refill
  - Poorly palpable pulses
- Signs of congestive heart failure:
  - Failure to thrive, poor feeding and diaphoresis
  - Increased respiratory work, chest wall retraction
  - Tachypnea, grunting
  - Gallop rhythm
  - Hepatomegaly

**Bedside monitoring data**

- ECG tracing: rhythm other than normal sinus
- Arterial waveform: blunted upstroke and narrow pulse pressure
- Atrial pressure change: see Box 31.3
- Urine output:
  - < 1.0 mL/kg/hour in neonates, infants, and children
  - < 25 mL/hour in older patients

**Laboratory and radiographic data**

- \( \text{SvO}_2 \): decreased (< 65–70%) with an increased (>30%) AVO\(_2\) difference
- Acid–base balance:
  - Metabolic acidosis with increased anion gap
  - Increased arterial lactate (>2.0 mM/L)
- Electrolytes:
  - Hyperkalemia
  - Elevated BUN and Cr
  - Increased liver transaminases
- Chest radiography:
  - Cardiac enlargement
  - Abnormal (increased or decreased) pulmonary blood flow
  - Pulmonary edema

\( \text{AV} \), arteriovenous; \( \text{BUN} \), blood urea nitrogen; \( \text{Cr} \), creatinine; \( \text{SvO}_2 \), systemic venous oxygen saturation.
and hepatomegaly. An increase in the arterial to mixed venous oxygen saturation (AVO2) difference of > 30% and a lactic acidosis provide biochemical evidence for low CO. The atrial pressure is a useful measure to follow, and both an increase and decrease could be observed in a LCOS. Factors that should be considered when evaluating the atrial pressure following surgery are shown in Box 31.3.

**Box 31.3: Factors that should be considered when there is a change in the measured atrial pressure outside of the anticipated range for a particular postoperative patient**

**Increased atrial pressure**
- Increased ventricular end-diastolic pressure
  - Decreased ventricular systolic or diastolic function
  - Myocardial ischemia
  - Ventricular hypertrophy
  - Ventricular outflow obstruction
  - Semilunar valve disease
- Mitral or tricuspid valve disease
- Large left-to-right anatomic shunt
- Residual ventricular septal defect
- Systemic-to-pulmonary artery connection
- Chamber hypoplasia
- Intravascular or ventricular volume overload
- Cardiac tamponade
- Dysrhythmia
  - Tachyarrhythmia
  - Complete heart block
- Artifactual
  - Catheter tip not in the atrium (e.g., in a ventricle, internal jugular pressure, or wedged in pulmonary vein)
  - Pressure transducer below level of heart or improperly calibrated or zeroed
  - Concomitant drug infusions through the atrial line

**Decreased atrial pressure**
- Inadequate preload
- Artifactual
  - Catheter malfunction (e.g., cracked or clotted)
  - Pressure transducer above level of heart, or improperly calibrated or zeroed

The mechanism(s) underlying low CO in a specific patient can be related to one or a combination of factors following surgery. Strategies for treating the patient with a low CO should focus on optimizing the balance between oxygen consumption (VO2) and delivery (DO2). In LCOS, oxygen and metabolic demand should be minimized by maintaining an adequate depth of analgesia and sedation, including chemical paralysis to avoid movement, and reduce muscle tone and oxygen debt. Strict avoidance of hyperthermia from any cause is essential, and in some circumstances, mild hypothermia may be preferable, although the effect of peripheral vasoconstriction and increase in SVR could have an adverse impact on myocardial wall stress and oxygen requirements.

**Surgical factors**

**Residual or unrecognized defects**

A thorough understanding of the underlying cardiac anatomy, surgical findings, and surgical procedures is essential because this will direct the initial postoperative evaluation and examination. Residual lesions may be evident by auscultation, intracardiac pressures and waveforms, and oxygen saturation data. For example, a large V wave on the left atrial waveform may indicate significant residual mitral valve regurgitation. An increase (step-up) of the right atrial to pulmonary artery oxygen saturation of more than 10% may indicate a significant intracardiac shunt across a residual VSD [31].

However, if there are significant concerns for important residual lesions that are compromising CO and ventricular function, further evaluation with echocardiography and/or cardiac catheterization should be considered. Imaging of the heart may be difficult immediately after surgery, because of limited transthoracic access and acoustic windows. During transthoracic echocardiography, it is important that hemodynamics are closely observed, because inadvertent pressure applied with the transducer may adversely affect filling pressures and mechanical ventilation. Similarly, vigorous antegrade flexion of a transesophageal echocardiography probe may induce pulmonary hypertension by altering left atrial filling by partial obstruction of a main-stem bronchus.

While surgery may be routine for many uncomplicated defects such as ASD closure, the approach for more complex intracardiac repairs may cause specific postoperative problems. For example, if a ventriculotomy is performed to close the VSD in a patient with TOF, RV dyskinesia and poor contraction may be apparent. On the other hand, if a transatrial approach had been used to close the VSD in the same patient, the risk for atrioventricular valve injury or dysrhythmias, such as junctional ectopic tachycardia and heart block, is increased. Often unexpected findings or technical difficulties at the time of surgery mean that modifications to the approach or procedure are necessary. A difficult procedure may lead to a longer time on CPB or additional traction on cardiac structures.

**Complications related to surgery**

Failure of adequate hemostasis may expose the patient to significant volumes of transfused blood products, and if there is inadequate drainage via chest drains placed at the time of surgery, the risk for cardiac tamponade is significant. This may be an acute event, but more commonly it is evident by progressive hypotension with a narrow pulse width, tachycardia, an increase in filling pressures, and reduced peripheral perfusion with possible evolving metabolic acidosis. A sudden decrease in chest tube drainage should raise the suspicion for potential tamponade. This is primarily a clinical diagnosis, and treatment (i.e., opening of the sternum) should not be delayed while waiting for echocardiographic confirmation.

Myocardial ischemia from inadequate coronary perfusion is often an under-appreciated event in the
postoperative pediatric patient. Nevertheless, there are a number of circumstances in which ischemia may occur, compromising ventricular function and CO. Myocardial ischemia may occur intraoperatively because of problems with cardioplegia delivery or insufficient hypothermic myocardial protection, and from intracoronary air embolism. In the CICU setting, mechanical obstruction of the coronary circulation is usually the cause of myocardial ischemia rather than coronary vasospasm. Examples include extrinsic compression of a coronary artery by an outflow tract conduit or annulus of a prosthetic valve, and kinking or distortion of a transferred coronary artery button. While electrocardiogram (ECG) changes may indicate ischemia (ST-segment abnormalities), a sudden increase in left atrial pressure or sudden onset of a dysrhythmia such as ventricular fibrillation or complete heart block may be an earlier warning sign.

**Cardiopulmonary bypass and the systemic inflammatory response**

The effects of prolonged CPB relate in part to the interactions of blood components with the extracorporeal circuit. This is magnified in children due to the large bypass circuit surface area and priming volume relative to patient blood volume. Humoral responses include activation of complement, kallikrein, eicosinoid, and fibrinolytic cascades; cellular responses include platelet activation and an inflammatory response, with an adhesion molecule cascade stimulating neutrophil activation and release of proteolytic and vasoactive substances [32–34].

The clinical consequences can include increased interstitial fluid, generalized capillary leak, and potential multiorgan dysfunction. Total lung water is increased with an associated decrease in lung compliance and increase in A–aO₂ gradient; some of these effects can be attenuated by modified hemofiltration [35,36]. Myocardial edema results in impaired ventricular systolic and diastolic function. A secondary fall in CO by 20–30% is common in neonates in the first 6–12 hours following surgery, contributing to decreased renal function and oliguria [37]. Sternal closure may need to be delayed due to mediastinal edema and associated cardiorespiratory compromise when closure is attempted. Ascites, hepatic congestion, and bowel edema may affect mechanical ventilation, causing a prolonged ileus and delay in enteral feeding. A coagulopathy post-CPB may contribute to delayed hemostasis. The clinical manifestation of some of these issues may be attenuated with the lower priming volumes and higher hematocrits used on modern bypass circuits (see Chapter 7 for a detailed discussion of the inflammatory response to CPB).

**Dysrhythmias**

The ECG is an essential component of the initial postoperative evaluation because the CICU team must identify whether the patient is in sinus rhythm early in the recovery period. If the rhythm cannot be determined with certainty from a surface 12- or 15-lead ECG, temporary epicardial atrial pacing wires, if present, can be used with the limb leads to generate an atrial ECG [38]. Also, right and left atrial waveforms are useful in diagnosing atrioventricular synchrony (see Chapter 18). Temporary epicardial atrial and/or ventricular pacing wires are routinely placed in many patients to allow mechanical pacing if sinus node dysfunction or heart block should occur in the early postoperative period. Because atrial wires are applied directly to the atrial epicardium, the electrical signal generated by atrial depolarization is significantly larger and thus easy to distinguish compared with the P wave on a surface ECG. Sinus tachycardia, which is common and often secondary to medications (e.g., sympathomimetics), pain and anxiety, or diminished ventricular function, must be distinguished from a supraventricular, ventricular, or junctional tachycardia. Any of these tachyarrhythmias can lower CO by either compromising diastolic filling of the ventricles or depressing their systolic function [39,40]. High-grade second-degree and third-degree (or complete) heart block can diminish CO by producing either bradycardia or loss of atrioventricular synchrony, or both. Third-degree block is transient in approximately one-third of cases. If it persists beyond postoperative day 9–10, it is unlikely to resolve, and a permanent pacemaker is indicated (see Chapter 18) [41].

**Low preload**

The diagnosis of insufficient preload is usually made by monitoring the mean atrial pressure or central venous pressure. The most common cause in the CICU is hypovolemia secondary to blood loss from postoperative bleeding. Initially after surgery and CPB, the filling pressures may be in the normal range or slightly elevated, but this often reflects a centralized blood volume secondary to peripheral vaso- and venoconstriction following hypothermic CPB. As the patient continues to rewarm and vasodilate in the ICU, considerable IV volume may be necessary to maintain the circulating blood volume. There may also be significant third-space fluid loss in neonates and small infants who manifest the greatest systemic inflammatory response following CPB. The “leaking” of fluid into serous cavities (e.g., ascites) and the extracellular space (edema progressing to anasarca) requires that these patients receive close monitoring and volume replacement to maintain the circulating blood volume. Patients with a hypertrophied or poorly compliant ventricle, and those with lesions dependent on complete mixing at the atrial level, also often require additional preload in the early postoperative period.

**High afterload**

Elevated afterload in both the pulmonary and systemic circulations frequently follows surgery with CPB [37,42].
Excessive afterload (SVR) in the systemic circulation results in diminished CO and is typically manifest by decreased peripheral perfusion and cool extremities. Treatment of elevated SVR includes recognizing and improving conditions that exacerbate vasoconstriction (e.g., pain and hypothermia) and administering a vasodilating agent. A vasodilator, which can be either a phosphodiesterase inhibitor (e.g., milrinone), a nitric oxide donor (e.g., nitroprusside), or a peripheral α-receptor antagonist (e.g., phenoxybenzamine or phentolamine), can be added to an inotropic agent such as epinephrine to augment CO. Neonates, who tolerate increased afterload less well than older infants and children, appear to derive particular benefit from afterload reduction therapy [43-45].

**Decreased myocardial contractility**

Because decreased myocardial contractility occurs frequently after reparative or palliative surgery with CPB, pharmacologic enhancement of contractility is used routinely in the CICU. Before initiating treatment with an inotrope, however, the patient’s intravascular volume status, serum ionized Ca\(^{2+}\) level, and cardiac rhythm should be considered. Inotropic agents enhance CO more effectively if preload is adequate, so IV colloid or crystalloid administration should be given if preload is low. If hypocalcemia (normal serum ionized Ca\(^{2+}\) levels are 1.14–1.20 mmol/L) is detected, supplementation with IV calcium gluconate or calcium chloride is appropriate, because Ca\(^{2+}\) is a potent positive inotrope itself, particularly in neonates and infants. Supranormal supplementation of calcium should be avoided however, as increased levels of diastolic myocardial calcium are potentially cytotoxic [46].

Dopamine can be the first-line agent to treat either mild hypotension (10–20% decrease in normal mean arterial blood pressure for age) or moderate hypotension (20–30% decrease in normal mean arterial blood pressure for age). This sympathomimetic agent promotes myocardial contractility by elevating intracellular Ca\(^{2+}\), both via direct binding to myocyte β\(_1\) adrenoceptors and by increasing norepinephrine levels. Dopamine is administered by a constant infusion because of its short half-life, and a usual starting dose for inotropy is 5 μg/kg/min. At a dose > 5 μg/kg/min, dopamine should be infused through a central venous catheter to avoid superficial tissue damage if extravasation were to occur. The dose is titrated to achieve the desired systemic blood pressure, although some patients, especially older children and adults, may develop an undesirable dose-dependent tachycardia. The challenge with dopamine is its simultaneous effects on β, α and dopaminergic receptors, often resulting in undesired rhythm disturbances despite maintaining an adequate blood pressure [47]. For this reason, low-dose epinephrine, up to 0.05 μg/kg/min is also a useful first-line inotropic agent and may have fewer arrhythmogenic side-effects than dopamine. If a patient does not respond adequately to dopamine up to 10 μg/kg/min or has severe hypotension (more than 30% decrease in mean arterial blood pressure for age), treatment with epinephrine should be considered.

Epinephrine should be given exclusively via a central venous catheter and can be added to dopamine at a starting dose of 0.01–0.05 μg/kg/min with subsequent titration of the infusion to achieve the target systemic blood pressure. At high doses (i.e., ≥ 0.2 μg/kg/min), epinephrine can produce significant renal and peripheral vasoconstriction, tachycardia, and increased myocardial oxygen demand (chronotropic and vasopressor effect) [43]. Patients with severe ventricular dysfunction who require persistent or escalating doses of epinephrine > 0.15–0.2 μg/kg/min may benefit from opening of the sternum and/or should be evaluated for the possibility of mechanical circulatory support with a ventricular assist device (VAD) or extracorporeal membrane oxygenation (ECMO) (see later).

A combination of epinephrine at lower doses (e.g., < 0.1 μg/kg/min) or dopamine with an IV afterload reducing agent such as nitroprusside or milrinone is frequently beneficial to support patients with significant ventricular dysfunction accompanied by elevated afterload. Norepinephrine is a direct-acting α agonist, primarily causing arteriolar vasoconstriction, but it also has positive inotropic actions. At doses of 0.01–0.2 μg/kg/min, it can be considered in patients with severe hypotension and low SVR (e.g., “warm” or “distributive” shock), inadequate coronary artery perfusion, or inadequate pulmonary blood flow with a systemic-to-pulmonary artery shunt. It is also useful in patients with preserved systemic ventricular function, but failing or inadequate RV contractility (pulmonary vascular obstructive disease or postoperative TOF with restrictive RV physiology). In patients with normal hearts, variation in afterload is accommodated by varying stroke volumes and contractility; the normal heart works at peak efficiency and contractility exceeds afterload. This increased contractility is also transferred to the RV through the shared intraventricular septum. The increased afterload also improves the filling characteristics of the LV (by shift of the interventricular septum) and augments RV coronary perfusion (especially in systemic RV pressure where the RV is now dependent exclusively on diastolic aortic root pressure for coronary perfusion). In the failing heart and in patients with limited ventricular reserve, an increase in afterload may not be matched by an increase in contractility, with a resultant fall in CO.

There can be a decrease in responsiveness to increasing doses of catecholamines over time; vasopressin at a dose of 0.01–0.05 units/kg/hour is a potent vasopressor that may help to improve the hemodynamics in advanced shock without compromising cardiac function or other adverse sequelae [48].

Patients who have the clinical features of relative adrenal insufficiency may benefit from stress steroid therapy [49,50]. This is primarily a clinical finding of poor
vascular tone with persistent hypotension and volume requirement that is refractory to increasing inotrope and/or vasopressor support. The serum cortisol level may be low or show a limited response to adrenocorticotropic hormone stimulation testing [51]; however, the ranges of normal have not been established for pediatric patients, in particular for newborns and infants after cardiac surgery. There is no consistent correlation between serum cortisol level and the incidence of LCOS; nevertheless, stress doses of hydrocortisone (50 mg/m²/day) have been associated with increased systemic blood pressure and lower inotrope scores, although they have not been definitively demonstrated to improve eventual survival. The increased risk for infection and poor wound healing dictates that stress dosing of steroids should be for a brief period of time (e.g., over 3–5 days) rather than continuing with a long taper [26].

Hypothyroidism is another cause for a persistent LCOS after cardiac surgery. Triiodothyronine (T₃) levels have been demonstrated to be low after CPB, and may remain low for up to 5 days after surgery, particularly if a sick euthyroid state develops and there is decreased conversion of thyroxine (T₄) to the biologically active T₃ in peripheral tissues [52,53]. A recent pediatric randomized, controlled trial evaluating protocolized treatment with T₃ (two doses of 0.4 μg/kg during surgery and three doses of 0.2 μg/kg at 3, 6 and 9 hours after cross-clamp release) demonstrated improvements in ejection fraction and time to extubation specifically in patients < 5 months of age [54].

Delayed sternal closure

Pericardial and sternal closure following cardiac surgery causes a restriction to cardiac function and can interfere with efficient mechanical ventilation. This is particularly important for neonates and infants, in whom considerable capillary leak and edema can develop following CPB, and in whom cardiopulmonary interactions have a significant impact on immediate postoperative recovery. In the operating room, mediastinal edema, unstable hemodynamic conditions from both systolic and diastolic dysfunction, and ongoing bleeding are indications for delayed sternal closure, although it may also be considered semi-electively for patients in whom hemodynamic or respiratory instability are anticipated in the immediate postoperative period (e.g., following a Norwood procedure for HLHS). Urgent reopening of the sternum in the CICU following surgery is associated with higher mortality compared with leaving the sternum open in the operating room, and successful sternal closure can be achieved for most patients by postoperative day 4 with a low risk for surgical site infection (SSI) [55]. Patients in whom this cannot be achieved and who have additional risk factors (e.g., neonate, need for ECMO, Norwood procedure) have an 11% SSI rate and significantly greater mortality [56]. Additional discussion of hemodynamic management is presented in Chapter 17.

KEY POINTS: MYOCARDIAL DYSFUNCTION AND HEMODYNAMIC MONITORING

- Low CO may be related to residual lesions, myocardial dysfunction, or a systemic inflammatory reaction related to bypass.
- An LCOS may result from adverse effects on rhythm, preload, afterload, or myocardial contractility.
- Restoration of circulating volume and vasoactive agents are first-line therapies. Corticosteroids and thyroid supplementation are second-line adjuncts.

Cardiopulmonary resuscitation in the CICU

Recognition of the high likelihood for cardiac arrest and need for cardiopulmonary resuscitation (CPR) are among the primary reasons for creating specialized units and teams such as pediatric cardiac critical care. The ability to rescue a patient from an event is often used as a metric of unit, team, and system performance, and it requires the thorough exchange of information, high-quality monitoring and resuscitative measures, and specific resources immediately available to facilitate resuscitation such as mechanical circulatory support. However, perhaps a better metric would be the ability of a team to anticipate and/or recognize an evolving clinical picture and prevent a critical event from occurring in the first place. A CPR event often flows through five phases. It is important to recognize the phase of care, as a vital therapeutic action in one phase is often detrimental in a subsequent phase.

Pre-arrest phase: monitoring and event risk reduction

The first role of critical care teams is to identify patients at risk for deterioration and cohort them in the ICU with anticipatory monitoring. This is straightforward for most postoperative surgical patients, but it becomes challenging for those patients who require inter-hospital transport or those in the emergency department or hospital wards. A rapid response or medical emergency team that is based out of the ICU is a useful adjunct to allow transition of a critically ill child to the ICU prior to a cardiac arrest [57–59]. Invasive (central venous and arterial blood pressure) hemodynamic monitoring combined with pulse oximetry and continuous ECG monitoring are the basics for any critically ill patient (medical or surgical). The importance of hemodynamic trends (e.g., progressive tachycardia and narrowing pulse pressure) and frequent confirmation by physical examination cannot be over-emphasized. A low invasive arterial blood pressure in a patient with clinically poor central and peripheral pulses is likely to be real, and cannot be explained simply as an issue with the monitoring system [60]. Additional
monitoring that is provided by blood gas and central venous oxygen sampling and echocardiography allow static and trend assessments that support the impression provided by physical examination and basic monitoring [61–63]. Near-infrared spectroscopy does not rely on pulse detection, and is thus useful in patients with a low output state who are at risk for cardiac arrest.

Use of capnography to monitor end-tidal CO$_2$ (EtCO$_2$) is especially valuable in patients with marginal CO or tenuous pulmonary blood flow dependent on an aortopulmonary shunt. Dramatic reductions (or loss) in EtCO$_2$ signals/tracings are often the first markers of the pre-arrest state or critical shunt obstruction [60].

Although LCOS can often be managed pre-emptively using inotropic therapy (see earlier), patients at risk for rapid deterioration often benefit from having low-dose boluses of either epinephrine (1 μg/kg or 0.1 mL/kg of 1:100,000) or phenylephrine (5 μg/kg) pre-prepared at the bedside. Provision of these drugs, for pre-established parameters, may rescue a failing circulation and prevent a cardiac arrest, thereby allowing time for other interventions, including sternal reopening or commencement of mechanical circulatory support.

Formation of formal resuscitation teams with clearly defined leadership, structure, roles and expectations is an important prerequisite in any critical care environment. Frequent simulation of resuscitation events is a key aspect to pre-arrest performance.

**Arrest phase: patient**

The goal is to recognize a loss of perfusing rhythm. Although presence of arterial pressure waveform and capnographic tracing can imply some amount of CO, the absence of palpable pulses is the *sine qua non* of cardiac arrest. Uncertainty or vagueness with pulses should err toward rapid, appropriate provision of CPR.

Maneuvers in the arrest phase include, but are not limited to, rapid securement of the airway, provision of appropriate levels of supplemental oxygen, reducing aggressive over-ventilation, providing hard and fast cardiac massage while allowing appropriate chest recoil, administering appropriate pharmacologic therapies, evaluating for inadequate lung (pneumothorax) or cardiac (tamponade) filling, and assessing for shockable rhythms. These therapies are continuously considered while assessing the response from objective monitoring (invasive arterial waveforms and quantitative EtCO$_2$) while minimizing interruptions in CPR.

There may be unique differences with the Pediatric Advanced Life Support guidelines in the conduct of CPR in patients with CHD. This is particularly the case in patients with single-ventricle physiology and a cavopulmonary connection. Sufficient time during chest recoil is needed to allow for pulmonary and cerebral blood flow. Even optimal closed-chest CPR results in cerebral blood flow that only approaches 25–30% of normal [64]. Other advanced interventions such as sternal reopening or ECMO need to be considered and mobilized early. Open-chest CPR can result in cerebral blood flows that approach or surpass normal [65].

**Post-resuscitation phase: patient**

After attaining hemodynamic stability, the goal of this phase is to optimize systemic oxygen and nutrient delivery (e.g. placing chest/pericardial drains, atrio- or ventricular pacing, optimizing vasoactive agents, volume and blood product replacement, and initiating mechanical support), while minimizing systemic oxygen consumption requirements through adequate sedation, muscle relaxation, and avoidance of hyperthermia.

A vital part of this phase is to assess the cause of the arrest and initiate measures to prevent a recurrence. The event may have been predictable based on the postoperative state and resuscitation with ECMO considered early. In contrast, the event may have been unanticipated and further investigation is required, such as through a cardiac catheterization or return to the operating room. It is important to discuss the appropriateness of potential interventions and, in some cases, recognize medical futility. These are appropriate discussions to have not only with relevant members of the medical/surgical team, but also with the child’s parents/guardians.

**Post-resuscitation phase: team debriefing**

Once the patient is stabilized and a care plan is devised and implemented, it is important to have a debriefing of the cardiac arrest event. This is easy to overlook in a busy intensive care environment. The ability to recognize deficiencies, improve performance, and prevent future cardiac arrests, however, is contingent on ensuring this process. It is important to debrief with the representative team in a safe environment through a systematic debriefing process [66]. Key aspects for broader dissemination (including process, personnel, and communication issues) should be documented (anonymously) in an effort aimed at continual improvement.

**Management of postoperative complications**

The unanticipated postoperative course requires critical review. Based on the anatomical diagnosis, the preoperative risk profile, and the intraoperative course (technical performance of repair, residual lesions of significance), one should be able to reasonably predict the postoperative course. If the course is different from that expected, it is incumbent on the CICU team to look actively for explanations. This may begin with repeat echocardiography or CT angiographic imaging; frequently, a cardiac catheterization provides vital information that leads to a return visit to the operating room (OR).
Such complications are often apparent early, but can often be masked by expert management until de-escalations of support result in obvious clinical deterioration. Other common postoperative complications can affect the process of ventilator weaning or recovery to hospital discharge (Box 31.4).

Box 31.4: Common postoperative complications

- Arrhythmias
- Bleeding
- Inability to wean from mechanical ventilation (see Box 31.1)
- Infection
  - Ventilator-associated pneumonia
  - Central line-associated bloodstream infection
  - Surgical site infection
- Chylothorax
- Thoracic duct injury
- Vocal cord injury
- Central venous thrombosis
- Seizures
- Intestinal ischemia (often referred to as necrotizing enterocolitis)
- Sedation/analgesia withdrawal
- Feeding intolerance

All pediatric cardiovascular programs should establish a process through which recognition and discussion of postoperative complications can occur. This allows identification of the patient who is not following an intended course and suggestions for evaluation and potential therapy. It also provides an opportunity to review key themes from a quality standpoint, ensuring critical attention to relevant processes (such as healthcare-acquired infection), as necessary.

Patient safety and quality improvement in the CICU

Vigilance and structured processes are vital to reduce or eliminate the risk of preventable injury. Critically ill patients require many decisions and processes to be efficiently delivered, and the environment is a key interface between human factors and technology. Although we are continually striving to improve the quality of care, every change in the system, despite people and/or technology, has the potential to adversely affect patient safety. The following general principles are fundamental to improving patient safety:

- Create a culture of transparency and respect.
- Measure performance continuously and provide timely data feedback to staff in a relevant format.
- Insist on clear, direct, and closed-loop communication.
- Limit interruptions as much as possible.
- Insist on systematic handovers during care transitions.
- Declare timeouts before invasive procedures.
- Ensure forced functions through appropriate human factor engineering of the environment (infusion pumps, alarm limits/silencing).

- Ensure read-backs and double checks when patient identification is key (blood products administration, transfer to OR).
- Create an anonymous, easy-to-use process for event reporting, review and resolution.

Essential to any environment that values patient safety is a culture of accountability, openness, and teamwork. One must balance the value of creating a blame-free environment (essential for recognizing mistakes) with ownership of the mistake as a team (and as the intensivist). The latter is key to creating accountability that results in measurable change when needed. Accountability also requires prompt disclosure of significant error(s) to the patient’s parents/guardian by the responsible attending intensivist. If these errors occurred outside of the CICU (e.g., operating room), the intensivist often plays a key role in facilitating disclosure by the appropriate individuals.

Mechanical support of the circulation

Mechanical assist devices serve an important role in the care of children with critical myocardial failure, providing stable circulatory support for patients who have become refractory to medical management. Support may be required for only a short period, allowing for recovery from a self-limited process (e.g., acute viral myocarditis or postcardiomyotomy myocardial failure), or may be needed for long-term support to bridge a patient to cardiac transplantation. Historically, ECMO has been the most common mode of mechanical support for patients in the CICU, and it continues to be a valuable tool secondary to its flexibility in cannulation strategy, ability to support both cardiac and pulmonary function, and ease of deployment. Over the last decade, there has been a dramatic increase in the use of VADs, as device manufacturers have created miniaturized pumps that can reliably support pediatric patients [67]. The experience with the Berlin Heart EXCOR® VAD, in particular, has demonstrated that pediatric patients can be successfully bridged to heart transplant with results that are comparable with the adult VAD experience [68]. Despite improvements in device design and increased clinician experience with these devices, significant morbidity and mortality are still seen in patients supported with mechanical assist devices, underscoring the need for further research to improve the care of this complex patient population.

Extracorporeal membrane oxygenation

Extracorporeal membrane oxygenation is the most widely used mode of mechanical cardiopulmonary support for children with CHD. It fully supports heart and lung function similar to CPB and requires significant levels of systemic anticoagulation to maintain circuit performance. Venoarterial ECMO is the most commonly employed support strategy in this patient population, as it provides cardiac support, but venovenous ECMO is occasionally
utilized when cardiac patients have primary respiratory failure. Figure 31.8 depicts a standard venoarterial ECMO circuit. Blood is drained from the right atrium (RA) by direct atrial cannulation, or from a superior vena cava (SVC) catheter advanced into the RA. When using a roller pump, the blood is first drained to a small venous reservoir; with a centrifugal pump, a reservoir is not used. Blood then passes through a membrane oxygenator and heat exchanger before returning to the ascending aorta, which is cannulated directly or via the right carotid artery. IVC, inferior vena cava; RV, right ventricle; PA, pulmonary artery; PV, pulmonary vein; LA, left atrium; LV, left ventricle.

Over the last two decades, there has been a progressive increase in the use of ECMO for cardiac indications, as increasingly complex surgical interventions are being performed in younger patients. Currently, there are over 500 children per year, worldwide, who receive ECMO for cardiac support [69,70]. The majority of these patients are placed on ECMO for postcardiotomy support, but other indications for ECMO include primary myocardial dysfunction secondary to cardiomyopathy or myocarditis, management of refractory arrhythmias, respiratory failure, refractory hypoxemia secondary to right-to-left intracardiac shunting, pulmonary hypertension, and for support during interventional cardiac catheterization or electrophysiology procedures in patients with unstable circulations. Overall survival to discharge is 40–50% in this heterogeneous group of patients, with certain subgroups demonstrating better outcomes [71]. Despite growing provider experience with ECMO, survival has remained largely unchanged over the last decade. Further refinements in patient selection, timing of deployment, and creation of more biocompatible circuits are needed to increase successful outcomes.

Extracorporeal membrane oxygenation plays an important role in the resuscitation of critically ill patients following cardiac surgical intervention. The best outcomes are seen in patients with a self-limited process, such as secondary myocardial failure following surgery with CPB [72]. These patients typically demonstrate recovery of myocardial function within 48–72 hours, as evidenced by the return of pulsatility on invasive arterial blood pressure monitoring and improved systolic performance on echocardiography. Venoarterial ECMO may also be an effective rescue therapy to bridge patients through correction of a reversible process, such as acute shunt thrombosis [73]. In patients who do not follow this pattern, further investigation, such as a comprehensive echocardiogram and/or cardiac catheterization, should be undertaken to search for potential residual defects. Although not without potential hazard, cardiac catheterization can be safely undertaken in this high-acuity population [74,75]. The outcome of patients who require ECMO secondary to an inability to wean from CPB in the operating room is particularly poor, with a reported survival of 10–30% [76,77]. Despite isolated case reports describing myocardial recovery following prolonged periods of support, several studies in the postcardiotomy population have demonstrated that survival is <10% in ECMO runs longer than 10–12 days [78].

Support of the single-ventricle patient can be problematic and merits further discussion. Outcomes in neonates with HLHS supported with ECMO following Norwood palliation are lower than other subpopulations, with hospital survival of 30% [79]. However, patients cannulated for severe hypoxemia, primarily secondary to shunt thrombosis, have better survival than patients supported for cardiac arrest or myocardial failure [73]. Patients with systemic-to-pulmonary artery shunts require unique management when supported by ECMO, as run-off through the shunt into the lung vessels will limit systemic blood flow and lead to impaired end-organ perfusion. Strategies for managing this circulation include increasing ECMO flow into the range of 150–200 mL/kg/min to provide increased systemic output or to occlude the shunt partially to limit pulmonary runoff. Complete shunt occlusion is not recommended and has been associated with worse survival [80]. ECMO support in patients with a cavopulmonary connection has also been associated with poor outcomes. One case series reported 17% survival for patients with a bi-directional Glenn circulation and a strong association with severe neurologic injury [81]. Neurologic injury is likely incurred secondary to the development of cerebral venous hypertension and impaired cerebral perfusion during low CO and/or CPR.

![Extracorporeal membrane oxygenation (ECMO) circuit](image-url)
That same case series report and a subsequent review of the Extracorporeal Life Support Organization (ELSO) registry for outcomes in Fontan patients revealed a 35% survival rate [81,82]. Patients who demonstrated evidence of Fontan failure immediately after surgery had better outcomes compared with patients who required ECMO for progressive myocardial failure. Patients with a cavopulmonary connection may require the insertion of an additional venous cannula in the upper body to optimize venous drainage, particularly if a femoral cannulation strategy is instituted.

Extracorporeal membrane oxygenation support for patients with acute fulminant myocarditis is associated with the highest survival rates in children requiring ECMO for cardiac indications [83]. Survival rates of 60–80% are reported in this subpopulation; these improved results are likely attributable to the typically reversible nature of the myocardial dysfunction, and the brief period needed to bridge to recovery. Myocardial recovery typically occurs within 2 weeks, and in those patients who continue to demonstrate severe myocardial dysfunction, conversion to a VAD for long-term support should be considered.

Extracorporeal membrane oxygenation may also be used to bridge patients to heart transplantation, but its role in this indication has been usurped by VADs in the current era. Survival to transplant in patients utilizing ECMO as a bridge has been reported to be 40–60%, compared with 70–80% in patients bridged with VAD support [84,85]. Given the limited number of available organs and increased waiting list times seen in pediatric patients, ECMO as a bridge strategy has limitations. Prolonged support with ECMO is associated with increasing complications, including bleeding, neurologic injury, end-organ failure, and sepsis.

Survival after pediatric in-hospital cardiac arrest is poor and reported to be 25–33% [86]. ECMO as part of CPR (ECPR) is increasingly used as a procedure to rescue children who do not recover spontaneous circulation during standard CPR. Initiation of ECPR is typically undertaken if there has been inadequate recovery with standard CPR following 10–15 minutes of resuscitation, provided there are no contraindications to mechanical support. Cannulation can be either through the chest, neck, or groin depending on the particular patient. A “clear” or asanguinous primed circuit will allow for more rapid deployment, but some centers use banked O-negative blood for circuit priming that is stored within their unit. A review of the ELSO registry reported a 38% hospital survival rate for ECPR, with patients who had an underlying cardiac diagnosis demonstrating more favorable outcomes [87]. There was no relationship between the type of cannulation strategy and survival. Interestingly, single-center reports of ECPR outcomes demonstrate better survival, suggesting that the development of experienced teams with structured protocols can yield improved results [88]. Long-term neurologic outcome data are lacking, but two studies report favorable neurologic outcomes in the majority of surviving patients [89,90].

A brief review of ECMO management principles follows. If time allows, blood is typically used to prime the ECMO circuit, but an asanguinous prime may be needed in the case of emergent deployment for ECPR. Traditionally, perfusionists have primed the ECMO circuit, but many centers now have trained ECMO specialists (nurses, respiratory therapists, physicians) to develop this skill set. Initially, the patient is supported with ECMO flows approaching full bypass flow (i.e., 100–150 mL/kg/min for patients in the range of 10 kg). This flow strategy allows for significant unloading of the myocardium and provides adequate perfusion to end organs to allow time for recovery. Inotropic agents are discontinued or minimized to decrease myocardial oxygen demand and to prevent down-regulation of adrenergic receptors in the myocardium and peripheral vasculature. Vasodilator agents may be necessary to control systemic hypertension in order to prevent bleeding and cerebral vascular events. A left atrial vent may be required in those two-ventricle patients who have an intact/restrictive atrial septum and do not demonstrate any native ejection, as left atrial hypertension and subsequent pulmonary hemorrhage will ensue. Ventilator support is adjusted to maintain FRC and minimize oxygen toxicity or barotrauma.

Anticoagulation is maintained with a heparin infusion beginning at 10–20 units/kg/hour, and it is titrated to maintain an activated clotting time (ACT) of 180–200 seconds. A lower ACT strategy may need to be utilized in a postoperative patient with significant ongoing bleeding. More recently, some centers are using heparin activity levels to assist with their anticoagulation management. Bleeding and coagulopathy are common, and blood products must be readily available for infusion into the circuit. The need for surgical exploration is common, particularly among postcardiotomy patients, with prior sites of surgical intervention and the cannulation sites themselves being potential sources of bleeding. Typically, a goal platelet count > 100,000, hematocrit > 35%, and a prothrombin time within the normal range are maintained in these patients. Epsilon-aminocaproic acid has been shown to be effective at reducing blood loss and transfusion in cardiac ECMO [91]. Recombinant factor seven has also demonstrated efficacy in reducing blood loss, but it can be associated with increasing thrombus burden in the circuit and thrombotic events in the supported patient [92]. Central nervous system (CNS) bleeding is a catastrophic complication and should be suspected whenever there is clinical and/or laboratory evidence of sudden blood loss without explanation. Cranial ultrasonography is a commonly used screening tool among infants supported on ECMO. Portable CT of the brain is a helpful tool to increase diagnostic yield, but is not widely available.

Inadequate ECMO circuit volume is indicated by excessive negative pressure readings on the venous side of the circuit and an inability to maintain target flows and mean arterial pressures. Pre- and post-oxygenator pressures are monitored to assess both oxygenator health and distal
resistance to flow. An increasing gradient between the pre- and post-oxygenator pressures in association with deteriorating gas exchange is an indication that oxygenator thrombosis has occurred. Increases in both pre- and post-oxygenator pressures indicate elevated distal resistance to flow secondary to mechanical issues with the arterial cannula or systemic hypertension.

Renal insufficiency and fluid overload can be managed by placement of a hemofilter in the circuit for continuous hemofiltration. If greater solute clearance is desired, hemodialysis can be run in tandem with the ECMO circuit. The development of acute renal failure while on ECMO has been associated with an increased risk for mortality [93]. However, use of continuous renal replacement therapy does not appear to confer risk for the development of chronic renal failure in the ECMO population [94,95].

Infectious complications are prevented by meticulous sterile technique, and broad-spectrum antibiotics are initiated if sepsis is suspected. Sedation, analgesia, and frequently paralysis are required for these patients to optimize patient comfort and minimize risk for cannula disruption. Nutritional support is frequently delivered parentally while on ECMO, although enteral nutrition may be provided in the absence of splanchnic hypoperfusion.

Extracorporeal membrane oxygenation support is weaned when the compromised myocardium has recovered, with the time course for recovery varying from as little as 24–48 hours to several weeks. Echocardiography (transthoracic, epicardial, or transesophageal) can be used to assess myocardial contractility both on full support and as support is weaned. Before weaning flow, inotropic agents are typically restarted or increased, intravascular volume status is optimized, and ventilator support is increased. As ECMO flow is progressively reduced, additional titration of cardiovascular and ventilator support will be required with frequent assessments of clinical CO. If repeated attempts at weaning are unsuccessful, the team and the parents/guardians must decide if support should be withdrawn or if further pursuit of long-term mechanical support and transplantation is appropriate.

**Ventricular assist devices**

The application of VAD technology has increased dramatically in the pediatric population over the last decade [96]. Historically, VAD use was limited because of technical considerations, including device size and increased risk of device thrombosis secondary to use of flows that were outside of the typical operating range (lower due to smaller patient size). Short-term devices were primarily used; these devices required patients to be sedated and supported with mechanical ventilation, limiting opportunities for rehabilitation. Currently, short-term VAD support is most often used in postcardiotomy patients with an ischemic myocardium secondary to an anomalous left coronary artery from the pulmonary artery (ALCAPA), patients with late repair of D-TGA and an intact ventricular septum who develop LV failure following arterial switch, or for temporary support of right ventricular failure following orthotopic heart transplantation or left ventricular assist device (LVAD) implantation [97].

With the arrival of the Berlin Heart EXCOR® pump and the creation of miniaturized continuous-flow devices, smaller pediatric patients can now be supported for longer periods and successfully bridged to heart transplantation. Long-term VAD support can be divided into paracorporeal pneumatic devices such as the Thoratec PVAD™ and Berlin Heart EXCOR®, or intracorporeal continuous flow devices such as the HeartWare® and HeartMate II®. The SynCardia Total Artificial Heart® is an intracorporeal pneumatic device that provides biventricular support, but its use has been limited to larger adolescents secondary to device size. The Berlin Heart EXCOR®VAD is the only one of these devices that has been specifically designed for a pediatric application and can support infants. Unlike the previously described short-term VADs, children with these devices can be weaned off sedation, extubated, and ambulate, allowing for pre-transplant rehabilitation. Larger patients whose body surface area permits implantation of the intracorporeal continuous-flow devices can be discharged from the hospital following intensive training in the daily maintenance of their device.

Despite relatively recent introduction into practice in the United States over the last decade, a large body of experience has developed with the Berlin Heart device. As compared with ECMO, patients can be supported for longer periods and more successfully bridged to transplant. The Berlin Heart investigational device exemption (IDE) trial reported that 88–92% of patients (two patient groups based on body surface area) were successfully bridged to transplant or recovery [68]. Serious adverse events included bleeding, infection, and stroke, which occurred in 29 % of the patients. A follow-up investigation examining all patients implanted with the Berlin Heart during the same study period as the IDE trial reported 75% survival to transplant or recovery [98]. Neurologic dysfunction occurred in 29% of the patients and was the leading cause of death. Smaller patient size, end-organ dysfunction pre-implantation, and biventricular support were all associated with increased risk of death while on VAD support. These findings underscore the importance of careful patient selection and timing of implantation.

A brief discussion of VAD management follows, but a more in-depth review can be found in Chapter 32. For the pneumatic devices, stroke volume is fixed and thus output is adjusted by titrating the beat rate of the device to provide an adequate clinical CO and blood pressure. In continuous-flow devices, the pump speed is titrated to achieve goal clinical CO and mean arterial pressure. Intravascular volume status and device filling can be monitored via central venous pressure and direct inspection for the paracorporeal devices, or via device
parameters in the intracorporeal devices. Systemic anticoagulation is necessary to prevent device thrombosis, but at a lower level than that required for ECMO. Patients are initially treated with heparin infusions and then transitioned to low-molecular-weight heparin or warfarin once they have recovered from device implantation and achieved stable VAD settings. Platelet inhibition with aspirin, dipyridamole, and/or clopidogrel may also be required to prevent thrombus formation, usually based on the manufacturer’s recommendations. For patients receiving LVAD support alone, medical support for the right ventricle is critical for optimizing post-implant care. Inotropic support and inhaled nitric oxide for RV afterload reduction are helpful adjuvants to assist with RV function. If the RV is unresponsive to medical therapy, mechanical RV support may be necessary with either a short-term or long-term device. This decision is frequently made either in the OR during LVAD implantation or within the first postoperative hours in the ICU.

**KEY POINTS: MECHANICAL SUPPORT OF THE CIRCULATION**

- ECMO is the most common mode of mechanical cardiac support utilized in the CICU secondary to its flexibility in cannulation strategy, ability to support both cardiac and pulmonary function, and ease of deployment.
- ECMO is most effective in patients with myocarditis, postcardiotomy myocardial failure, or shunt thrombosis. Prolonged support with ECMO is associated with increasing complications, including bleeding, neurologic injury, end-organ failure, and sepsis.
- ECMO may be used as an adjunct to assist with resuscitation of patients who do not recover spontaneous circulation during standard CPR. Long-term neurologic outcome data are lacking for this patient group.
- Increasing experience with VAD use has improved the care of patients with terminal heart failure who are awaiting transplantation. Patient selection and timing of device implantation are critical in optimizing patient outcomes.

**Hemostasis**

The risk of postoperative bleeding in the pediatric cardiac surgical patient is multifactorial. Delayed hemostasis can be partly related to the deleterious inflammatory and hematologic effects of CPB which include hemodilution from the bypass circuit prime, stimulation of the intrinsic coagulation pathway resulting in coagulation factor consumption, and platelet activation and aggregation leading to platelet loss and dysfunction [99]. Priming the bypass circuit with reconstituted whole blood has been demonstrated to be beneficial in neonates and infants undergoing cardiac surgery to reduce post-bypass bleeding [100]. Patient-specific factors identified as risks for postoperative bleeding include low CO with tissue hypoperfusion and associated disseminated intravascular coagulopathy, hepatic immaturity or dysfunction, the preoperative use of anticoagulants and antiplatelet agents, a history of prior cardiac surgery, the presence of extensive suture lines, and chronic cyanosis.

Prompt identification and scrupulous control of surgical bleeding are essential in preventing the complications associated with massive transfusion. Postoperative bleeding is traditionally categorized into three groups on the basis of chest tube output. Output < 5 mL/kg/hour is usually associated with minor disturbances in coagulation status and typically resolves spontaneously. Drainage of 5–10 mL/kg/hour is more concerning and requires aggressive medical management with volume resuscitation, mainly in the form of blood product replacement. Persistent postoperative bleeding > 10 mL/kg/hour, despite normalization of the coagulation profile and platelet count, demands prompt communication with surgical colleagues and consideration of chest re-exploration.

Evaluation of the integrity of the coagulation system postoperatively includes laboratory assessment of prothrombin time, partial thromboplastin time (PTT), fibrinogen level, and platelet count. Additional testing including a PTT incubated with heparinase may provide further insight regarding the presence of residual heparin as a source of bleeding. Transfusion of platelets, fresh frozen plasma, and/or cryoprecipitate to correct coagulopathy and platelet dysfunction or thrombocytopenia is an important initial intervention. Normalization of body temperature (i.e., eliminating hypothermia) and correction of hypocalcemia can be helpful adjuncts in achieving hemostasis. Evidence of a prolonged PTT with a normal heparinase-treated sample suggests the presence of residual heparin and can be corrected with an additional dose of protamine. Antifibrinolytic agents such as epsilon-aminocaproic acid and tranexamic acid are used intraoperatively to reduce bleeding, but may also be effective in the ICU if coagulopathy and fibrinolysis persist [101]. These agents bind to plasminogen, rendering it incapable of binding to lysine residues on fibrin and thus inhibiting plasmin generation. Recombinant activated factor seven has also been used in cases of refractory postoperative bleeding with salutary effects on chest tube output and blood product usage, but it has also been associated with significant risk of thrombosis [102,103]. Factor VIII inhibitor bypass activity is a prothrombin complex concentrate that has been used in a fashion similar to recombinant factor seven in adults with similar efficacy and morbidity [104,105]. Reports of its use in the pediatric population have been limited to abstract form in a population of patients on mechanical support [106]. Its usage was associated with achievement of hemostasis and there were no thrombotic events or device malfunctions. Chapter 13 has an extensive presentation of bleeding and hemostasis in CHD surgery.
Infection control

Hospital-acquired infections are an important source of morbidity and mortality in ICUs, and they cause increased healthcare expenditure [107,108]. Patients in CICUs are particularly vulnerable secondary to the high incidence of surgical procedures, exposure to the inflammatory and immunomodulatory effects of CPB, and the routine use of invasive devices. Bloodstream infection and SSI are the most common, followed by ventilator-associated pneumonia and urinary tract infection [109,110]. Studies examining risk factors for nosocomial infection frequently identify younger age, higher disease complexity (e.g., based on RACHS-1 and PRISM scores), and the presence of delayed sternal closure as factors that convey increased risk [109–111]. An analysis of central line-associated bloodstream infection in a CICU identified the presence of central venous line duration for 7 days or more, hydrocortisone use, blood product exposure ≥ 3 units, the presence of non-cardiac co-morbidities, and non-elective admission to the ICU as risk factors (Box 31.5) [26]. Reviews of SSIs identify younger age, inappropriate timing of prophylactic antibiotics, excessive bleeding in the immediate postoperative period, and prolonged CPB as important risk factors [112,113]. In the setting of delayed sternal closure, multiple episodes of delayed sternal closure and ECMO use have been identified as independent risk factors for SSI [56].

Efforts at limiting the occurrence of nosocomial infection have focused on staff education, hand hygiene, creation of central line insertion and maintenance bundles, daily evaluations of the need for all indwelling devices (e.g., central venous line, Foley catheter, endotracheal tube), and regular audits of staff compliance. When trialed, these maneuvers have proved successful and led to decreasing rates of infection [114]. Additional maneuvers to minimize SSI have included a preoperative chlorhexidine bath prior to the day of surgery, standardizing intraoperative skin preparation and antibiotic timing, standardization of dressing care, early removal of pacing wires, and utilization of sterile technique for transthoracic echocardiograms in fresh postoperative patients [112]. Given the previously identified risks of steroid use and exposure to blood products, future studies may investigate the efficacy of limiting these interventions in CICU patients.

Neurologic monitoring/assessment and complications

Surgical mortality for patients with CHD has progressively declined over the last several decades, yielding a growing population of survivors who display an incidence of neurologic, developmental, and psychiatric disabilities that are notably greater than normal healthy children [115]. In particular, children who undergo repair or palliative procedures as neonates and infants appear to be the group at greatest risk [116]. These emerging data reinforce the importance of further refining pre-, intra-, and postoperative care to minimize potential neurologic insults to the developing brain.

Historically, children with CHD but no associated genetic disorder were believed to have normal brain development. This precept has been challenged over the last decade with new studies utilizing advancements in magnetic resonance imaging (MRI) technology. MRI studies have demonstrated the presence of brain immaturity and white matter abnormalities prior to any surgical intervention [117]. These findings have been documented most consistently in patients with D-TGA and severe left
ventricular outflow obstruction, particularly variants of HLHS [118]. Changes in fetal circulation related to the presence of these congenital heart lesions appear to cause these abnormalities, although future research is necessary to confirm causality [119].

While patients with CHD may have coexisting CNS abnormalities, they are also at risk of acquired neurologic injury throughout the perioperative period when surgery is required. These injuries may occur due to periods of hypoxia/ischemia, CNS hemorrhage, and embolic phenomenon. Premature infants are at additional risk for intraventricular hemorrhage. Older patients, particularly those with chronic cyanosis, are at risk for injury secondary to cerebral abscess and stroke, the latter related to venous or arterial thrombosis from erythrocytosis. In light of data illustrating the presence of pre-existing brain injury, attempts to mitigate damage related to these perioperative insults take on even greater importance.

A large body of research over the past several decades has contributed to advances in intraoperative management with the goal of decreasing brain injury related to bypass and surgery. These include the application of deep hypothermia to minimize injury during periods of ischemia, controlling the rate of body cooling and rewarming, optimizing perfusion pressure and flow via bypass, minimizing periods of circulatory arrest or avoiding it altogether with regional brain perfusion, optimizing hematocrit, adjusting pH and PaCO₂ during periods of hypothermia (pH stat strategy), and refining bypass circuit technology to minimize the risk for particulate or air emboli [120–122]. In addition, intraoperative monitoring with near-infrared spectroscopy (NIRS) to assess regional cerebral oxygen saturation has assisted in avoiding prolonged episodes of hypoxia/ischemia, particularly during periods of circulatory arrest or regional cerebral perfusion [123]. Some centers may also use transcranial Doppler assessment during regional perfusion to assess adequacy of bypass flow [124,125].

Postoperative monitoring and care in the CICU also play a critical role in avoiding neurologic insults. Postoperative factors contributing to neurologic injury are related mainly to the development of a persistent LCOS with depressed cerebral perfusion and potential progression to cardiovascular collapse. Assessment of CNS function may prove difficult, particularly in patients receiving sedation and/or muscle relaxants. The extension of the intraoperative practice of monitoring cerebral oximetry via NIRS to the CICU has allowed for a further portal into assessing the interplay between hemodynamics and the CNS. Several studies have demonstrated that sustained periods with low postoperative cerebral oxygen saturation (below a range of 45–55% by oximetry) are associated with poor outcomes, particularly in the HLHS population [126–128]. Some institutions have instituted protocols to alert intensivists when these threshold values are reached; interventions are then initiated, such as volume resuscitation, increased inotropy, modulation of afterload/vascular resistance, and increased sedation to minimize oxygen demand [129]. Further studies are needed to validate the efficacy of these protocols. Additional factors in patient management may play an important role in avoiding neurologic injury, including minimizing hyperventilation (to prevent reduction in cerebral blood flow) and avoiding hyperthermia. Post-bypass hyperthermia may develop from low CO with associated peripheral vasoconstriction or from aggressive rewarming practices. Judicious control of brain temperature after ischemic injury has been shown to influence delayed neuronal death and subsequent neurologic recovery following traumatic brain injury. Data from a neonatal porcine model of circulatory arrest also demonstrated the detrimental effect of hyperthermia on neurologic outcome [130]. Avoidance of hyperthermia in the postoperative period may help to attenuate neurologic injury associated with circulatory arrest and periods of low output in the CICU [131]. Use of therapeutic hypothermia has been implemented to positive effect in neonatal hypoxic–ischemic brain injury and in adults following witnessed cardiac arrest due to ventricular fibrillation [132,133]. Its use has been extended to pediatric patients following cardiac arrest, but there is currently no evidence demonstrating its benefit [134]. Several randomized clinical trials are underway to assess the efficacy of this intervention.

Seizures were the most frequently observed neurologic complication following deep hypothermic circulatory arrest (DHCA), with a reported incidence of 4–25% [135]. Both focal and generalized seizures have been described, usually occurring on the first or second postoperative day. Status epilepticus was uncommon, and the occurrence of postoperative seizures did not increase the risk for seizures later in life. The Boston circulatory arrest study demonstrated that early postoperative seizures are a marker for worse neurodevelopmental outcome [136]. In recent years, postoperative seizures have become a rare event, with an incidence of 4%, which is likely secondary to improved techniques for neurologic protection as described in the above discussion [137]. Other potential inciting events for postoperative seizures include embolic phenomenon and cardiac arrest with development of severe hypoxic–ischemic injury. As stated previously, clinical detection of seizures in the CICU can be impaired by the presence of sedation and paralysis, necessitating careful assessment of autonomic manifestations such as sudden onset of tachycardia, hypertension, and pupillary dilation, although the cause of these signs is difficult to distinguish from other hemodynamic causes. Acute declines in cerebral oximetry may also be noted, but as this technique assesses regional oxygen saturation, it may not reliably detect seizure activity in areas remote from the frontal cortex. Electroencephalogram (EEG) monitoring is a useful adjunct in the diagnosis of seizures; in particular, 24-hour video EEG monitoring can be helpful in assessing subtle or clinically silent seizure activity (non-convulsive status epilepticus). Imaging with head CT and/or MRI may be instructive, particularly if the seizures...
are focal in nature, suggesting the presence of a localized lesion such as an intracerebral hemorrhage. Treatment of postoperative seizures includes first-line administration of a benzodiazepine, typically lorazepam, followed by administration of fosphenytoin for persistent seizure activity [138]. Additional agents, including phenobarbital, levetiracetam, and a continuous midazolam infusion, may also be employed for refractory status epilepticus.

Stroke is another neurologic complication seen in the CICU. Awareness of this clinical entity has been heightened, as mechanical support with VADs has become the standard of care for end-stage heart failure. Other potential risk factors for stroke include the presence of intracardiac thrombus in association with ventricular dysfunction and arrhythmia, right-to-left intracardiac shunt, chronic cyanosis with associated erythrocytosis, artificial valves, anticoagulant/antiplatelet use, and inherited or acquired thrombophilia [99]. Careful history and physical examination are important to establish timing of the event, potential contributing risk factors, and the nature/severity of the neurologic deficits. Parents are often astute observers of subtle changes in their children, and their insights should be elicited. Initial signs and symptoms are age-dependent, with infants less than 6 months old typically demonstrating non-specific signs such as altered mental status (persistent irritability or depressed level of consciousness) and seizures. Older children may display focal neurologic findings, such as hemiparesis, which are associated with specific vascular territories. Cerebral venous thrombosis typically yields non-specific findings across all age groups, with depressed mental status, headache, vomiting, and seizures being typical symptoms. Subsequent management includes neurodiagnostic imaging with head CT and brain MRI to assess for hemorrhage with the former, and focal areas of ischemia/infarction with the latter. Cerebral vascular imaging may add further diagnostic information. Treatment involves efforts to restore or optimize perfusion to affected areas, modify risk factors, if possible, and deliver additional supportive care (mechanical ventilation if the airway cannot be protected). Use of thrombolytics and anticoagulation is guided by a careful analysis of the risk/benefit ratio of these therapies, including risk for hemorrhage into the recently infarcted area.

Choreoathetosis is an increasingly uncommon, yet sometimes devastating, complication following cardiac surgery in children with or without the use of DHCA. It has been reported in the neonate, but is more common in older infants. Factors thought to contribute to the development of choreoathetosis include inadequate brain cooling (particularly to deeper structures such as the basal ganglia and midbrain), rapid rate of cooling, alpha-stat blood gas strategy during cooling, and the presence of systemic-to-pulmonary artery collateral vessels, which may result in cerebral steal [139,140].

Longitudinal follow-up of neonates and infants who have undergone cardiac surgery demonstrates that the risk of long-term neurodevelopmental abnormalities is most likely the result of an interplay among pre-existing brain injury, perioperative risk factors, and patient-specific factors (e.g., type of congenital heart lesion, socioeconomic status, gestational age, presence of genetic abnormalities). Prolonged length of stay in the CICU has also been associated with worse cognitive outcomes, even when adjusted for perioperative events and sociodemographic variables [141]. Neurodevelopmental abnormalities appear to be most pronounced in the single-ventricle population, especially those with HLHS [115,142]. Motor deficits are significantly worse than cognitive deficits at 1 year of age. More sophisticated testing can be performed in older patients, and detailed follow-up of the Boston Circulatory Arrest Study group in adolescence revealed impairments in memory, visual-spatial skills, executive function, attention, and social integration [143]. A significant proportion of these patients also required academic and behavioral services, with 33% receiving tutoring and 25% receiving special education. Children with repair of congenital heart defects, in later infancy and childhood, have had more encouraging neurodevelopmental results, with one study demonstrating test results within the population normative range [144]. These long-term assessments of neurodevelopment underscore the need for the creation of integrated support systems, including physical/occupational therapy, academic support, and psychological counseling to assist these at-risk children following hospital discharge. Chapter 11 has an extensive discussion of neurological monitoring and outcomes.

KEY POINTS: NEUROLOGIC MONITORING/ASSESSMENT AND COMPLICATIONS

- Children who undergo surgical intervention as neonates and young infants appear to be at the greatest risk for the subsequent development of neurologic, developmental, and psychiatric disabilities.
- Neonates with CHD, particularly those with D-TGA and severe left ventricular outflow tract obstruction, frequently demonstrate evidence of brain immaturity on MRI.
- Prolonged length of stay in the CICU is associated with worse cognitive outcomes, even when adjusted for perioperative events and sociodemographic variables.
- The clinical manifestations of stroke are age-dependent, with infants typically demonstrating altered mental status and seizures, while older children display focal neurologic deficits associated with specific vascular territories.
Fluid management and renal dysfunction

Fluid overload and renal dysfunction are important sources of morbidity and occasional mortality in the CICU. Data from the general pediatric critical care population reveal that increasing degrees of fluid overload are an independent predictor of pulmonary dysfunction and increased length of hospitalization [145]. A subsequent evaluation in the postoperative cardiac population demonstrated similar findings and was associated with poor response to diuretic therapy [146]. The inflammatory effects of CPB often lead to an increase in total body water, with capillary leak and interstitial fluid accumulation continuing for the first 24–48 hours after surgery. Intravascular depletion leads to progressive hemodynamic compromise and necessitates ongoing volume replacement with crystalloid, colloid, and/or blood products. The youngest patients, particularly neonates and young infants, who tend to have longer CPB support times, are the population at greatest risk for the development of capillary leak syndrome [147]. Subsequent development of a LOS or increased secretion of anti-diuretic hormone contribute to delayed water clearance and potential renal dysfunction, which may progress to renal failure, particularly if the low output state persists.

Management of fluid overload begins in the operating room through the initiation of ultrafiltration. Ultrafiltration is a technique that removes low-molecular-weight solutes and plasma water through convection using hydrostatic forces to filter these substances across a semipermeable membrane. The use of modified ultrafiltration has been shown to reduce fluid accumulation in the early postoperative period, decrease postoperative blood loss and blood product use, improve lung compliance with decreased duration of mechanical ventilation, and improve ventricular function [148–152]. Intraoperative glucocorticoids have also been used for many years to blunt the inflammatory effects of CPB, but while decreasing laboratory evidence of inflammation, this intervention has not been shown to make a significant change in clinical outcomes [153].

Fluid management post-CPB in the CICU commences with restriction of maintenance IV fluids to 65–75% of full maintenance and is coupled with judicious use of fluid replacement titrated to appropriate filling pressures and hemodynamic response. Once the patient has achieved greater hemodynamic stability and the capillary leak process has subsided, IV diuretics are instituted to accelerate fluid removal and assist with the reduction in mechanical ventilator support. Furosemide (1 mg/kg IV every 6–8 hours) is a commonly prescribed loop diuretic that must be excreted into the renal tubular system before producing diuresis. Low CO therefore reduces its efficacy. Bolus dosing may result in a significant diuresis over a short period, resulting in intravascular depletion and potentially in hypotension. A continuous furosemide infusion (0.1–0.3 mg/kg/hour) after an initial bolus dose may provide a more consistent and sustained diuresis without inducing sudden fluid shifts. Chlorothiazide (5–10 mg/kg IV or PO every 6–12 hours) is also an effective diuretic, particularly when used in conjunction with loop diuretics. Low-dose dopamine (3–5 μg/kg/min), in addition to supporting CO, may increase renal blood flow and promote diuresis. Fenoldopam (0.1–0.5 μg/kg/min), a selective dopamine-1 receptor agonist, may also assist in optimizing diuresis by reducing renal vascular resistance and enhancing renal perfusion [154]. Nesiritide (0.005–0.03 μg/kg/min), a recombinant form of brain natriuretic peptide (BNP) identical to endogenous BNP, can also be considered as an adjunct to encourage diuresis. Its cardiac effects include increased lusitropy through a reduction in cytosolic calcium leading to cardiac myocyte relaxation, while in the kidney it promotes diuresis through afferent arteriolar vasodilation and efferent arteriolar vasoconstriction. There are limited reports of its use in the pediatric population, but these studies suggest that it can be used safely in the pediatric heart failure population to promote diuresis [155,156]. Caution is advised in the use of nesiritide, as administration has been associated with worsening renal function and risk for mortality in adults with decompensated heart failure [157,158].

Acute kidney injury (AKI) occurs commonly in the CICU, with a reported incidence of 15–52% [159–162]. This wide range of reported incidence is probably due to use of differing criteria to define AKI, as well as examination of different study populations. The two most commonly used criteria to define AKI are the pediatric application of the adult RIFLE criteria (pRIFLE: risk, injury, failure, loss of kidney function, and end-stage kidney disease) and the Acute Kidney Injury Network (AKIN) criteria (Table 31.4). Patients are grouped into the first three categories (corresponding to AKI) based on progressive declines in urine output and estimated creatinine clearance via the Schwartz equation. The AKIN criteria define three stages based on progressive increases in serum creatinine from baseline, with a minimum increase of 0.3 mg/dL, and categorize any patient receiving renal replacement therapy as failure. Although the reported incidence of AKI is variable, multiple studies report that younger patients, particularly infants, with exposure to prolonged durations of CPB are the population at greatest risk for the development of AKI [159,161]. Two large, single-center reports also indicate that single-ventricle physiology is an independent risk factor for AKI [160,162]. Most patients develop mild degrees of AKI by postoperative day one and recover within 2–3 days. Patients with increasing severity of AKI are more likely to have prolonged mechanical ventilation and longer ICU/hospital stays [159–161].

While serum creatinine has traditionally been used as the gold standard for the assessment of renal function, assessments of AKI based on increases in serum creatinine may delay diagnosis and render interventions ineffective, as renal injury occurs well before changes in creatinine levels can be measured. Extensive basic and translational
Definition/classification of pediatric and adult acute kidney injury (AKI)

<table>
<thead>
<tr>
<th>Class</th>
<th>pRIFLE</th>
<th>eCrCl by Schwartz</th>
<th>Adult RIFLE</th>
<th>AKIN</th>
</tr>
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<tbody>
<tr>
<td>Risk</td>
<td>&lt;0.5 mL/kg/hour x 8 hours</td>
<td>eCrCl decrease by 25%</td>
<td>Risk</td>
<td>&lt;0.5 mL/kg/hour x 8 hours</td>
</tr>
<tr>
<td>Injury</td>
<td>&lt;0.5 mL/kg/hour x 16 hours</td>
<td>eCrCl decrease by 50%</td>
<td>Injury</td>
<td>&lt;0.5 mL/kg/hour x 16 hours</td>
</tr>
<tr>
<td>Fail</td>
<td>&lt;0.3 mL/kg/hour x 24 hours or Anuric x 12 hours</td>
<td>eCrCl decrease by 75% or &lt;35 mL/min/1.73 m²</td>
<td>Fail</td>
<td>&lt;0.3 mL/kg/hour x 24 hours or Anuric x 12 hours</td>
</tr>
<tr>
<td>Loss</td>
<td>Failure &gt;4 weeks</td>
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<td>Loss</td>
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<td>ESRD</td>
<td>Failure &gt;3 months</td>
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<td>ESRD</td>
<td>Failure &gt;3 months</td>
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</tbody>
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Abbreviations: AKIN, Acute Kidney Injury Network; eCrCl, estimated creatinine clearance; ESRD, end-stage renal disease; GFR, glomerular filtration rate; pRIFLE, pediatric RIFLE; RIFLE, Risk, Injury, Failure, Loss and End-Stage; SCr, serum creatinine; ↑, increase.

Source: Cooper et al. [147]. Reproduced with permission of Sage.

Science research has yielded the discovery of several emerging biomarkers that may allow for a more rapid diagnosis of AKI. The best-described biomarkers include neutrophil gelatinase-associated lipocalin (NGAL), cystatin C, interleukin-18 (IL-18), liver fatty acid-binding protein (L-FABP), and kidney injury molecule-1 (KIM-1). All of these biomarkers have been studied in the post-CPB population, and in single-center studies have been shown to be independent predictors of AKI [163,164]. When these same biomarkers were evaluated in prospective multi-center observational studies, they did not perform as well, particularly in discriminating mild AKI, but continued to be predictive of more severe degrees of AKI [165,166]. Further research is ongoing regarding the use of biomarkers in the diagnosis of AKI and their potential for the evaluation of therapeutic interventions.

There are currently no recognized medical therapies for the treatment of AKI in the pediatric population. N-acetylcysteine (NAC) has known antioxidant properties and has been used historically to prevent or attenuate renal injury related to IV contrast exposure for radiologic studies. Multiple randomized, placebo-controlled studies in adults have failed to demonstrate any clear benefit of NAC in the prevention of AKI, and its use for this purpose in the pediatric population has not been reported [167]. Aminophylline in a single-center retrospective study has been reported to improve renal excretory function and augment urine output in CICU patients with oliguric AKI [168]. A randomized, placebo-controlled study examining aminophylline use in the postoperative pediatric cardiac population is ongoing.

When AKI progresses to renal failure, renal replacement therapy may be indicated to treat fluid overload, severe electrolyte or metabolic derangements, symptomatic uremia, and fluid restriction limiting the delivery of adequate nutritional support. A peritoneal dialysis (PD) catheter may be placed either for simple drainage with the goal of reducing intra-abdominal pressure or for the institution of true peritoneal dialysis. Several centers have reported prophylactic placement of peritoneal dialysis catheters with early institution of dialysis in the immediate postoperative period to relieve fluid overload [169,170]. Both studies reported shorter time to achievement of negative fluid balance, decreased duration of mechanical ventilation, and decreased inotrope scores. Complications of PD catheter placement and use include infection and injury to abdominal organs. In addition, a persistent communication among the peritoneum, mediastinum, and/or pleural cavities early following surgery may limit the effectiveness of peritoneal dialysis. Double-lumen, large-bore catheters (minimum 7 Fr in size) may also be placed in a large systemic vein to institute intermittent hemodialysis or continuous veno-venous hemofiltration and dialysis (CVVH/D). As postoperative cardiac patients frequently will not tolerate the larger fluid shifts generated through intermittent hemodialysis, CVVH/D is typically the modality of choice. CVVH/D is more efficient than PD in both fluid and solute removal. Complications related to this therapy include infection, catheter-related venous thrombosis, and potential hemodynamic instability related to fluid shifts. Although there are no CICU-specific studies regarding CVVH/D, multiple studies in the general pediatric intensive care population report an association between mortality and increasing degrees of fluid overload, suggesting that earlier initiation of this therapy may be beneficial [171,172].
Nutrition and gastrointestinal complications

Adequate delivery of nutrition is a vital component in the care of critically ill children. Several studies in the pediatric and adult critical care population have underscored the importance of nutrition therapy by demonstrating its role in reducing the incidence of infection, duration of mechanical ventilation, and length of stay [173–175]. Despite the importance of optimizing nutritional intake, there are often multiple barriers to the delivery of adequate calories to patients in the CICU. These barriers include dynamic changes in energy expenditure, particularly in the early postoperative period, and the need to impose restrictions in fluid intake secondary to capillary leak and renal dysfunction. Parenteral nutrition is frequently employed in the early postoperative period secondary to concerns regarding systemic or splanchnic hypoperfusion and feeding intolerance. As in the critically ill adult population, stress ulceration and gastritis can occur in pediatric patients. Prophylaxis with H₂-receptor blocking and proton pump inhibitor drugs should be considered in any patient requiring significant vasoactive and mechanical ventilator support. Post-anesthesia nausea and vomiting is a frequent occurrence in the early postoperative period, particularly in patients who have been fast-tracked to extubate either in the OR or within several hours of arriving in the CICU. Use of antiemetics, such as 5-HT₃-receptor antagonists, H₁-histamine receptor antagonists, benzodiazepines, and anticholinergics may be helpful in mitigating this response.

Early resumption of enteral nutrition is encouraged to reduce the risk of nosocomial pulmonary and bloodstream infections by preventing bacterial overgrowth and to minimize complications associated with the delivery of enteral nutrition, including catheter-related infection and liver injury or cholestasis. The use of feeding algorithms has been demonstrated to improve the introduction of enteral nutrition following cardiac surgery (Figure 31.9) [176,177]. Unfortunately, the introduction of enteral nutrition can be compromised by the presence of splanchnic hypoperfusion due to a LCOS or from low diastolic pressure in patients with run-off from systemic-to-pulmonary artery shunts, or large PDA in the preoperative period. Clinical manifestations of splanchnic hypoperfusion range from feeding intolerance and ileus to necrotizing enterocolitis [178]. The onset of abdominal distension, bloody stool, and pneumatosis intestinalis on abdominal radiograph suggest necrotizing enterocolitis. Severe cases may also demonstrate signs of abdominal wall cellulitis, sepsis, hemodynamic instability, and gut perforation. Initial treatment includes discontinuation of enteral feeds, support with pentereral nutrition, and broad-spectrum IV antibiotics [179]. Hemodynamic support may be necessary, and occasionally laparotomy if perforation occurs or hemodynamic instability persists.

Other causes of feeding intolerance in the pediatric cardiac population include bowel edema following CPB, delayed gastric emptying secondary to opioid use for perioperative analgesia, gastroesophageal reflex, vocal cord dysfunction, and small bowel obstruction secondary to malrotation, particularly in the heterotaxy population [180,181]. Patients with decreased ventricular function may be unable to increase their CO sufficiently to meet the metabolic demand associated with oral feeding and the absorption of food. Coexisting respiratory problems such as tachypnea may also restrict oral intake. Placement of an enteral feeding tube is helpful to ensure adequate nutritional intake in these circumstances. Transition from nasogastric to transpyloric feeding may also be considered in patients with delayed gastric emptying, respiratory compromise requiring non-invasive PPV with accompanying gastric insufflation, and severe gastroesophageal reflex. In addition, progressive increases in the caloric density of enteral feeds (e.g., from 20 to 30 kcal/ounce) are frequently required to meet patient metabolic demands and prevent fluid overload. Consultation with a registered dietician, assessment of somatic growth by measuring serial weights, analysis of nutritional status via biochemical markers (i.e., albumin, pre-albumin, and transferrin), and consideration of indirect calorimetry to assess resting energy expenditure can assist in ensuring the adequate delivery of calories [182].

Liver dysfunction may also occur in CICU patients. It is typically related to a persistent LCOS causing ischemic hepatitis or complications related to CPB, including inadequate venous drainage from the lower body and low perfusion pressure. Patients following a Fontan procedure
Figure 31.9 Boston Cardiovascular Program Enteral Feeding Algorithm. TPN, total parenteral nutrition; NG, nasogastric. (Source: Braudis et al. [176]. Adapted with permission of RNC Publishing.)

may be at particular risk because of hepatic venous congestion from persistently elevated central venous pressure. Marked elevations in liver transaminases may be detected within hours of surgery and remain elevated for 2–3 days before gradually returning to normal. These patients typically have elevated prothrombin time and PPT as well, and are thus at increased risk of bleeding complications. However, fulminant hepatic failure is uncommon.
KEY POINTS: NUTRITION AND GASTROINTESTINAL COMPLICATIONS

- Patients in the CICU are often malnourished from the catabolic state induced by CHF and postoperative stress, as well as fluid restriction secondary to capillary leak and renal dysfunction.
- Enteral nutrition may be compromised by splanchnic hypoperfusion due to low CO or from low diastolic pressure in patients with run-off systemic-to-pulmonary artery shunts.
- The use of feeding algorithms has been demonstrated to improve the introduction of enteral nutrition following cardiac surgery.

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A full reference list for this chapter is available at:
http://www.wiley.com/go/andropoulos/congenitalheart

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CHAPTER 32
Mechanical Support of the Circulation

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Background, introduction, and history

The successful use of extracorporeal membrane oxygenation (ECMO) in children began in the late 1970s when Bartlett et al. applied this technology to term newborn infants with respiratory failure [1]. In 1973 Soeter et al. described the use of ECMO for cardiorespiratory failure after tetralogy of Fallot correction [2], and in 1987 Kanter et al. reported the first series of 13 patients with postoperative cardiac failure treated with ECMO [3]. The utilization of ECMO for cardiac support has increased steadily since the 1980s [4–6]. Improved perfusion and anticoagulation techniques make the support safer so that it may be initiated earlier and not as a last resort. Data from the Extracorporeal Life Support Organization (ELSO) reveal an increase in ECMO support for cardiac failure over the past 5 years, from 897 cases in 2007 to 1,368 cases in 2012. There is also greater use in older pediatric patients, with the percentage of neonatal patients decreasing from 41% in 2007 to 22% in 2012, and the percent > 16 years of age increasing from 21% to 52% over the same period. The survival rate has remained relatively constant at around 45–50% of patients [6].

The first successful use of a ventricular assist device (VAD) as a bridge to heart transplant in an adult was reported by Cooley et al. in 1969 [7]. The first description of VAD use in children was 20 years later [8], and the authors concluded that, like adults, VAD could be used as a bridge to cardiac transplantation in children. In the 1990s, VAD use in children was sporadic. However, due to improvements and miniaturization of equipment, VAD implantation in children has grown exponentially [9,10].
**Indications for mechanical support**

Mechanical support can be considered for children with potentially reversible cardiac failure, respiratory failure, pulmonary hypertension, and cardiopulmonary arrest. When used for cardiac failure, the primary goal is to rest the myocardium to allow recovery of function (bridge to recovery). In the absence of recovery of the myocardium, the patient may be transitioned to long-term mechanical support while awaiting a heart transplant (bridge to transplant) [11]. Adult patients can have a permanent mechanical device to support the circulation for the remainder of their lives (destination therapy). There is no such destination therapy device in pediatrics at present. The indications for mechanical circulatory support (MCS) in children are often divided into two groups: those related and those unrelated to cardiac surgery (Box 32.1).

**Box 32.1: Indications for mechanical support in neonates, infants, and children**

**Indications related to cardiac surgery**
- Preoperative stabilization and support
- Postoperative support
  - Failure to wean from cardiopulmonary bypass
  - Low cardiac output state
  - Respiratory failure
  - Severe hypoxemia (blocked shunt or right-to-left shunt)
  - Cardiac arrest

**Indications unrelated to cardiac surgery**
- Respiratory failure (oxygenation and/or ventilation failure)
- Septic shock
- Cardiovascular indications
  - Myocarditis
  - Cardiomyopathy
  - Intractable arrhythmias
  - Instability during cardiac catheterization
  - Pulmonary hypertension
  - Intoxicants
  - Aid to organ donation
  - Cardiac arrest

As a general principle, ECMO could potentially be used for all the indications in Box 32.1, and VAD only considered in the absence of pulmonary hypertension or respiratory dysfunction. There are pros and cons of VAD and ECMO devices, and they are often used in sequence; however, either device can be used as a bridge to recovery or a bridge to transplant. The choice depends on acuity of illness, co-morbidities, potential for recovery, and anticipated duration of support [12]. In addition, if there is a choice between ECMO and VAD, a left ventricular assist device (LVAD) is preferable if patients are suspected of needing longer than 2 weeks of circulatory support and if the support is intended as a bridge to transplant. As ECMO has become safer, it is generally agreed that mechanical support should be initiated early, before circulatory collapse in order to avoid prolonged periods of low cardiac output state (LCOS) and organ hypoperfusion. Patients with cardiac dysfunction after cardiopulmonary bypass (CPB) have a better prognosis when ECMO is initiated in the operating room (OR), rather than waiting for deterioration in the pediatric intensive care unit (PICU). In one study of 81 children, those placed on ECMO in the OR had a survival rate of 64%, whereas those put on ECMO in the PICU had a 29% recovery [13].

**Preoperative stabilization and support**

Occasionally, neonates with severe cyanosis or cardiogenic shock require preoperative mechanical support for stabilization before proceeding to the OR. There are many case reports of successful use of ECMO in this context [14]. At Royal Children’s Hospital and Texas Children’s Hospital, we have numerous successful anecdotal examples of preoperative ECMO use, yet no studies showing superiority of this approach.

**Failure to wean from CPB or LCOS after cardiac surgery**

Failure to wean from CPB after congenital heart surgery is the most common cardiac indication for mechanical support [15], and it is estimated that 2–5% of all children require ECMO after congenital heart surgery [16]. Extracorporeal cardiac life support may be required after CPB due to a LCOS, respiratory failure or severe hypoxemia (due to right-to-left shunt or blocked systemic-to-pulmonary artery shunts). The etiology of a LCOS after CPB may be anatomical (and must be excluded by echocardiography or sometimes catheterization), ventricular dysfunction (often due to long CPB and cross-clamp times), arrhythmias, or pulmonary hypertension. Mechanical support could be required immediately on attempted separation from CPB, or may be required later and used as rescue in intensive care. If mechanical support is initiated in the OR, the cannulas are often placed in the right atrium and aorta via the sternotomy. If it is initiated in the ICU, commonly the neck vessels are used (internal jugular and common carotid), unless the child had a recent sternotomy and it is faster to reopen the chest.

Criteria for considering ECMO or VAD in patients with LCOS include a progressive increase in inotrope or vasopressor dosage with evidence of poor end-organ perfusion, such as reduced mixed venous oxygenation (<40%, reduced cerebral saturation (>20% below baseline), oliguria, or metabolic acidosis. Again, initiation of early mechanical support in these situations shows better outcomes [11].

Patients with single-ventricle physiology or cyanotic heart disease are more likely to require mechanical support after CPB. According to the ELSO registry 2015, the most frequent congenital heart disease (CHD) requiring ECMO in neonates is hypoplastic left heart syndrome (HLHS), with 33% survival of stage 1 palliation surgery, although generally those who require ECMO for hypoxia (often
a blocked shunt) have a better outcome than those who require support for low cardiac output. [17]

**Resuscitation of cardiac arrest**

Resuscitation of children with ECMO during cardiopulmonary resuscitation (CPR) for cardiac arrest was first described in 1992. del Nido et al. reported on the use of venoarterial ECMO for 11 children with a witnessed sudden cardiac arrest. Ten out of 11 patients were centrally cannulated and seven patients survived to hospital discharge. Using extracorporeal support for management of cardiac arrest is termed “extra-corporeal cardiopulmonary resuscitation” (ECPR) [18]. The American Heart Association (AHA) 2010 resuscitation guidelines state, “There is increasing evidence that extracorporeal cardiac life support (ECLS) can act as a bridge to maintain oxygenation and circulation in selected infants and children with cardiac arrest if they are transplant candidates or have a self-limited or treatable illness” [19]. When compared with CPR alone, it appears that ECPR improves survival by 12–23% in children [20]. ECPR is typically only effective when arrest occurs in a highly monitored environment (such as the ICU), and in an institution that can rapidly deploy suitable expertise and equipment. Typically two ECMO circuits need to be ready and primed with a balanced salt solution at all times, one for patients < 10 kg and one for patients > 10 kg. These circuits can be maintained sterile for up to 4 weeks, with albumin or blood added immediately before use if required. The AHA (2010) state there is no good evidence for an upper limit as to the length of CPR after which ECPR should be considered futile; it is known that long-term survival is possible after > 50 minutes of CPR [21].

A recent review of the ELSO registry for term and premature neonates receiving ECPR from 1998 to 2010 revealed 39% survived to discharge, however gestational age, corrected gestational age and birth weight correlated inversely with stroke and death. Of those born before 34 weeks, the survival was 21%. As expected, if dysrhythmia was the primary diagnosis, the odds of death were significantly lower than those with single-ventricle physiology. Overall, the survival rate was similar to that of older children receiving ECPR [22].

**Respiratory failure and lung transplantation**

When considering mechanical support for respiratory failure, neonatal patients are typically differentiated from (older) pediatric patients due to different etiologies and pathophysiology. With neonates, the conditions requiring ECMO are either acquired at birth or congenital in origin, such as meconium aspiration, pulmonary hypoplasia (possibly with congenital diaphragmatic hernia), pneumonia/septicaemia, and persistent pulmonary hypertension of the newborn [23]. Of these neonatal causes, congenital diaphragmatic hernia is the most common reason for the use of ECMO with 51% survival [6]. Overall the use of ECMO in the neonatal population decreased in the 1990s due to advances in ventilation strategies (including high-frequency oscillation) and medical management such as nitric oxide [24]. However, the rate of ECMO use for persistent pulmonary hypertension and congenital diaphragmatic hernia has remained steady. Currently in total, approximately 800 neonates require ECMO support annually [6].

Older pediatric patients require ECMO because of acquired conditions such as pneumonia (bacterial, viral or fungal), aspiration, acute respiratory distress syndrome (ARDS), or acute respiratory failure from other causes [6]. Today many pediatric patients requiring ECMO have significant co-morbidity, such as renal, lung, and heart disease. In an ECMO registry review, 19% of these patients had co-morbidities in 1993, compared with 47% in 2007 [25]. Because of a lack of randomized controlled trials, the use of ECMO as a treatment modality has been slowly accepted [26], and recent evidence demonstrates accelerated interest from new advances in equipment/technique. For example, veno-venous cannulation has reduced the need for carotid puncture and therefore reduced the risk of neurological complications [25].

Technically, ECMO could be used as a bridge to lung transplantation; however, long waiting times on ECMO are associated with morbidity and mortality from bleeding at the cannulation or surgical entry sites, hemolysis and coagulopathy, sepsis and multi-organ failure. It is known that the survival of pediatric patients having ECMO as a bridge to heart transplant is significantly better than for lung or heart–lung transplant [27]. ECMO is therefore not favored for long-term use as a bridge to lung transplant. New machines such as the pumpless lung assist devices (described later) may alter the risk–benefit assessment of mechanical support in these patients. After lung transplant, patients who develop primary graft dysfunction may require extracorporeal support. Both veno-venous and venoarterial ECMO can be used, allowing the lungs to recover from the acute injury with an overall rate of survival to discharge of 42% [28].

**Sepsis**

Septic shock may be the primary reason requiring mechanical support, or sepsis could be a coexisting problem in a patient with respiratory or cardiac failure. This causes classification difficulties, which can pose a problem for extracting meaningful outcome data. Despite this, sepsis was historically considered a contraindication for ECMO; however, it is now accepted that ECMO is a viable therapy in neonates and children. In neonates, the survival rates are approximately 80%, whereas in older children the data are more limited, but the rate is expected to be about 50% [29]. The prognosis may be changing with improving ECMO technology [30]. The American College of Critical Care Medicine has issued a consensus statement on the management of children with septic shock, suggesting that ECMO be considered when a child is deteriorating from
hypotension, rising lactate, or progressive multi-organ dysfunction despite high doses of vasoactive/inotropic medications, aggressive fluids, and appropriate medical management [29]. During this assessment, the rate of progression of shock with associated physiological decline is more important than the absolute amount of inotropic support [30].

Myocarditis, cardiomyopathy, and cardiac transplantation

In children without CHD, viral myocarditis is the commonest cause of acute heart failure. ECMO is the initial modality of choice for MCS, because of ease of application, biventricular support, and, relatively few complications [31]. Once on mechanical support, ECMO can be used as a bridge to VAD, transplant, or recovery. ECMO in this population was first reported in 1999 with an 80% survival [32]. Duncan et al. reported on 15 patients who were put on mechanical support with acute fulminant myocarditis. Of these, 12 were put on ECMO, two on LVAD and one on biventricular VAD (BiVAD). Overall, nine patients (60%) were subsequently weaned from support and seven survived. The remaining six were bridged to transplant, of whom one died. In the 2015 ECLS registry report, the survival rate for myocarditis requiring ECMO is 49% for neonates, 72% for children aged 1–12 months and 71% for those aged 1–16 years [17].

Extracorporeal membrane oxygenation is also used in children with dilated or restrictive cardiomyopathy in order to bridge to transplant. Although venaarterial ECMO has traditionally been the standard management strategy, recent reports have supported the use of paracorporeal pulsatile VAD to reduce waiting list mortality [34–36]. Using the Berlin Heart EXCOR® VAD (Berlin Heart, GmbH, The Woodlands, Texas, USA), 73 patients were retrospectively analyzed in a multicenter study. Of these, 70% were successfully bridged to transplant and 7% bridged to recovery [37]. With VAD techniques and technology improving, ECMO is no longer used for long-term bridge strategy in these patients [38].

Extracorporeal membrane oxygenation is also used for patients with early and late ventricular dysfunction after cardiac transplant. In a series of 310 transplant recipients, 28 required early venaarterial ECMO (within the first 2 days of transplant) [39]. In a recent retrospective chart review of 100 pediatric orthotopic heart transplant recipients, 15 patients required 17 episodes of ECLS. Ten of these episodes were early (<1 month after transplant) and seven were late (>1 month). Of the 10 with early graft failure, eight were weaned from support with graft function recovery, one was retransplanted, and one died. Late failure was due to acute rejection and had a 50% mortality [40]. ECMO is usually the initial mode of support because of the speed of application and familiarity, as well as the ability to manage circulations with right ventricular dysfunction and high pulmonary vascular resistance (PVR). [27].

Arrhythmias with hemodynamic compromise

Short-term mechanical support can be used for malignant arrhythmias while medical management is optimized or ablation performed. Etiology includes post-cardiotomy arrhythmia, myocarditis, or cardiomyopathy. It is important that coronary ischemia is excluded as a cause.

Cardiac catheterization instability

Improvement in skills and equipment has led to a greater number of younger, sicker patients presenting for complex interventional procedures in the catheterization laboratory. ECMO has been used as rescue therapy after a critical event, or can be used prophylactically to manage a LCOS. Patients at greatest risk include those < 1 month of age with poor cardiovascular performance. Four high-risk hemodynamic variables include: high end-diastolic pressure, low systemic arterial saturations, low mixed venous saturations, and high pulmonary artery pressures [41]. In one reported series, 57% of children receiving ECPR in the catheterization survived to discharge [42].

Pulmonary hypertension

Three groups of patients with pulmonary hypertension may be considered as candidates for ECMO support. The first group are perioperative patients with reversible pulmonary hypertension, e.g., neonates with total anomalous pulmonary venous drainage whose elevated PVR would be expected to improve with time after surgical correction. The second group includes those with severe pulmonary hypertension who are at high risk of an acute pulmonary hypertensive crisis from intervention or illness (e.g., cardiac catheterization or intercurrent illness). Ideally, the decision regarding suitability of ECMO as rescue for such patients is made before the pulmonary hypertension crisis. Even centers with an expert mechanical support team report low survival with ECPR in these patients [38]. The third group includes patients with severe medically refractory pulmonary hypertension who require venaarterial ECMO as a bridge to heart–lung or lung transplant; however, the likelihood of survival with this approach is quoted as “minimal” [9], and should be made on a case-by-case basis. Novalung® (Novalung GmbH, Hechingen, Germany) has recently developed a paracorporeal pumpless interventional lung assist device that uses a low-resistance hollow-fiber oxygenator (usually without a heat exchanger). This device has been applied to patients with cardiogenic shock from pulmonary hypertension, with cannulas placed via sternotomy in the pulmonary artery and left atrium. High pulmonary pressures drive the blood through the oxygenator, without the need for a mechanical pump, removing CO₂ and improving oxygenation. Pulmonary pressures are reduced, which offloads the failing right ventricle, potentially allowing right ventricular recovery. Four patients, aged 15–41
years, were successfully bridged to transplant [43]. The application of this technology in younger patients is still under development; however, in a recent report, four infants, aged 9–22 months, with chronic lung disease and pulmonary hypertension were supported with this technology. One was bridged to recovery, one was bridged to lung transplant and two died (at 54 and 72 days) while awaiting organs [44]. A potential advantage of these pulseless devices is that they are considerably smaller than the currently available ECMO circuits and therefore may have a role in the transport of critically ill patients.

Intoxicants
A recent literature review identified 46 reports, from 1996 to 2012, where ECMO was used in both adult and pediatric patients with ARDS or circulatory shock from poisoning. The most common intoxicants cited were beta-blockers and calcium channel blockers; however, other drugs mentioned were ibuprofen, tricyclic antidepressants, colchicine, and chloroquine [45]. ECMO is considered good salvage therapy in these patients, although the overall mortality is difficult to ascertain.

Mechanical support to assist organ donation
With a worldwide shortage of donor organs, there is potential for extracorporeal support to improve organ perfusion and increase the availability of viable organs suitable for transplant. Cultural and legal barriers differ depending on the country concerned; however, mechanical support has been used to improve viable organ retrieval in both brain-dead donors and in donation after cardiac death (DCD) [46,47]. Brain-dead donors have been supported with ECMO after suffering cardiac arrest or severe cardiovascular or respiratory dysfunction before organ retrieval. The timing of the implementation of ECLS cannulation for DCD, before or after declaration of circulatory death, depends on the institution. The aim is to reduce warm ischemia time and improve the chance of graft survival. Firm conclusions regarding organ outcomes using this technique are difficult to draw in this population at this stage [48].

**KEY POINTS: INDICATIONS FOR MECHANICAL SUPPORT**

- Mechanical circulatory support should be initiated early, before organ injury from a low cardiac output state. Criteria include:
  - Progressive increase in inotropes or vasopressors with continued poor tissue perfusion
  - Mixed venous oxygen saturation < 40%
  - Cerebral saturation < 20% below baseline

- Oliguria
- Metabolic acidosis
- The American College of Critical Care Medicine states that ECMO should be considered in the treatment of children with septic shock unresponsive to inotropes and fluid management.

**Contraindications to mechanical support in children**

It is difficult to provide absolute numerical “cut-offs” as to who should categorically not be offered mechanical support. Contraindications are related to either futility of treatment or an unacceptably high risk of death or severe long-term morbidity. As medical equipment and techniques evolve, the risk–benefit balances change. It is therefore wise to consider the suitability of individual patients on their own merits. For example, infants with HLHS were once considered very poor candidates for ECLS, but now this is the most common congenital heart lesion requiring mechanical support of the circulation [49].

FUTILITY of mechanical support refers to the presence of a lethal anomaly, either cardiac or non-cardiac in origin. An example could include lethal chromosomal disorders, severe irreversible brain damage (e.g. hypoxic–ischemic encephalopathy), or unrecoverable cardiac or respiratory injury. Of course, “unrecoverable” is patient- and organ-specific, and the definition of futility in the context of ECMO remains very difficult [50].

Malignancy has also been considered under this “futile” category in the past, although the outcome of children with cancer is quite good [51]; however, patients with neutropenic sepsis following bone marrow transplantation have a particularly bad prognosis [52,53]. Despite this, a recent report described the successful use of ECMO in a few of these children [54]. Another group considered to be “futile” are those with advanced multi-organ failure. However, MacLaren et al. describe 23 children at high risk of death from septic shock, of whom 22 had failure of at least three organ systems. All were cannulated centrally through the chest in order to obtain higher flow rates, and 17 patients (74%) survived to discharge. [55] This high-flow technique appears to confer greater survival than with conventional ECMO.

Neonates pose a particular difficulty in defining contraindications. The ELSO registry shows that neonates have good survival for all diagnoses. However, certain neonatal subsets pose a particular risk when considered for ECMO, because of the risk of developing or worsening intracranial hemorrhage (ICH), i.e., low birth weight, extreme prematurity and pre-existing ICH. Those with low gestational age (<32–34 weeks) are at greatest risk. Most bleeds occur in the first 72 hours after birth, so in theory the risk of ICH and hemorrhage extension may be less after the infant is 3 days old. It is known that grade 3 ICH (blood causing enlargement of the ventricles) and
grade 4 ICH (blood extending into the brain parenchyma) confer a poor long-term prognosis [56]. ECMO increases the risk of extension of pre-existing ICH, and most ECMO exclusion criteria include those with ICH grade 3 or 4. Although neonates with ICH < grade 3 have potential for hemorrhagic extension, it is feasible to manage these patients without worsening of their ICH, provided there is imaging and diligent monitoring of their coagulation status [57]. One study reports a 6% incidence of ICH in babies < 2 kg compared to 4% in those > 2 kg [58]. Technical considerations would also make ECMO difficult in small neonates, such as the availability of small enough cannulas to provide adequate flow. It is highly possible that the high incidence of ICH on ECMO reported in the earlier trials [59] would not be reflected with today’s more evolved management of ECMO. In the absence of good long-term developmental follow-up data, many would currently consider birth weight < 1.6 kg as a reasonable contraindication to ECMO. A regression analysis suggested that 1.6 kg was the lowest threshold weight to achieve a 40% survival in non-cardiac ECLS [58]. Although some have suggested ECLS to be beneficial in neonates > 32 weeks gestational age [60], many consider a gestational age < 34 weeks to be a relative contraindication to ECMO [57]. As data emerge, these thresholds change; neonates < 2.5 kg still demonstrate mortality rates after cardiac surgery greater than that of larger neonates, but survival remains at > 70% in this high-risk group [61]. Examining ECPR in neonates, the survival was 21% for those < 34 weeks gestational age and 20% for those < 2 kg. Yet these findings do not support a strict age cut-off for ECPR [22]. With the above caveats in mind, a list of contraindications is presented in Box 32.2.

Box 32.2: Contraindications for mechanical support in neonates, infants, and children

**Neonatal population**
- Severe irreversible CNS injury
- Lethal congenital abnormality (cardiac or non cardiac anomaly)
- Intraventricular hemorrhage grade 3 or 4
- Gestational age <34 weeks
- Very low birth weight e.g. <1.6 kg
- Uncontrollable coagulopathy

**Infants and older children**
- Severe irreversible CNS injury
- Incurable malignancy
- Advanced multisystem organ failure
- Irreversible organ damage if not suitable for transplantation

CNS, central nervous system.

Note that extreme prematurity and very low birth weight are risk factors for intracranial hemorrhage on mechanical support.

Futile treatment in the context of repeated or prolonged ECMO is a difficult issue. It is known that the probability of ECMO survival in children with respiratory failure reduces with the number of days on support. We also know that myocardial recovery is rare after 12 days of ECMO support after pediatric cardiac surgery. Despite this, prolonged ECLS has produced some remarkable outcomes in children, so delineating ‘futility’ is poorly defined. Logically, it is therefore suggested that repeat ECMO should not be offered unless the mechanical support was originally withdrawn prematurely or a new treatment modality is considered [62].

In addition to those in Box 32.2, other relative contraindications can occur in specific circumstances, such as patients with congenital diaphragmatic hernia in the presence of complex CHD, or patients with severe myocardial dysfunction not suitable for transplantation [63]. Some patients have case-specific poor prognostic features, such as hyperkalaemia in the context of hypothermic arrest. This may indicate irreversible cell damage and potassium leakage and therefore a poor chance of recovery [64].

**Devices**

**Extracorporeal membrane oxygenation**

The first generation of ECMO devices used a silicon oxygenator membrane, roller pump, and simple arterial and venous cannulas. Newer technology provides hollow-fiber oxygenators with a much lower resistance across the oxygenator membrane. Therefore, centrifugal pumps are now more commonly used. Finally, there has been significant research toward improving the biocompatibility of the circuit surface. Today, the simplified modern ECMO circuit has a significantly smaller priming volume and can be managed by a trained ICU nurse. The Royal Children’s Hospital (RCH) in Melbourne, Australia, began using centrifugal pump ECLS in 1989. Their experience is described below.

**The pump**

In 1992 a hemolysis trial comparing the Biomedicus Biopump® (Medtronic Corp., Minneapolis, MN, USA) centrifugal pump with a conventional roller pump [65] found that the roller pump produced notably more hemolysis at 24 hours with a linear increase over time; however, by day 5 of use, the Biomedicus acutely begins to cause cell trauma approaching the severity of the roller pump at 7 days. This trial confirmed the clinical experience at RCH of electively replacing the Biomedicus at day 5 as a precautionary measure, or earlier if indicated. In the 1990s, the Rotaflow® pump (Maquet Medical Systems, Wayne, NJ, USA; Figure 32.1) was developed with many theoretical advantages over the Biomedicus. The pump rotor is suspended and driven by a radial permanent magnetic field that stabilizes the impeller in four of the six spatial degrees of freedom and allows it to be top-spun on a single blood flushed pivot bearing with minimal load and friction. This pump has a small internal volume, and surface and passage time demonstrate excellent hydraulic efficiency. It can provide 10 L/min of pump flow rate against 400 mmHg of total head pressure, indicating
The CentriMag® (Levitronix, Zürich, Switzerland), which features bearing-less technology, has also been successfully used for ECMO in Europe. The rotor is levitated into the housing by the magnetic force generated by the motor, hence minimizing friction and improving hemocompatibility. The risk of thrombus formation is reduced by uniform unidirectional flow and less stagnation, while reduced shearing stress attenuates hemolysis. In a simulated model of pediatric ECLS, retrograde flow was demonstrated to occur at low rotational speeds in the CentriMag, the Biomedicus, and the Rotaflow. At lower pump speeds, the CentriMag pump exhibited both the earliest occurrence and the greatest degree of retrograde flow amongst the pumps [68].

The oxygenator

Hollow-fiber oxygenators such as the QuadroxD (Maquet Medical Systems, Wayne, NJ, USA) became available in 2000 and this device revolutionized practice in a number of ways, as it has one of the lowest pressure drops across the oxygenator [69]. By making the oxygenator more compact, and optimizing blood flow path, the surface area of the membrane and heat exchanger is smaller, which reduces the potential for thrombus formation and inflammatory activation. The device itself has a maximally rated blood flow of 7 L/min with a 250 mL prime volume. This low prime volume enables the use of one device for all patient sizes, and a circuit can be left assembled with an asanguineous prime for emergent use. This oxygenator does not demonstrate plasma leakage necessitating circuit change, which we feel aids in lung recovery and hemostasis.

Recently other companies have begun to produce hollow-fiber oxygenators, e.g., the Medos Hilite® (Medos Medizintechnik AG, Heilbronn, Germany) 7000LT (275 mL priming volume), 2400LT (95 mL priming volume) and 800LT (55 mL priming volume). These have the same fiber technology and inherent benefits as the QuadroxD, but allow a smaller prime volume that can potentially provide asanguineous ECMO support for neonatal patients.
Thromboresistant surfaces
The aim of thromboresistant surfaces is to inhibit activation of the inflammatory and coagulation systems from blood exposure to the foreign surface of the ECLS. To this end, the materials composing circuits must be as hemocompatible as possible. Hemocompatibility refers to those properties that allow ECLS circuits to maintain contact with flowing blood without producing adverse reactions. These attributes depend not only on the surface characteristics of a given material, but also on extrinsic conditions such as sites of cannulation, duration of contact with blood, and local hemodynamic status (e.g., pulsatile vs. non-pulsatile flow, length and diameter of tubes) [70, 71]. When surfaces feature peaks or valleys (average height or depth = 9 μm), the number of platelets adhering to polyvinylchloride (PVC) surfaces is increased threefold, compared with polished surfaces [71, 72].

Heparin coating of the ECLS circuit would theoretically improve hemocompatibility. In addition, albumin priming of the ECMO circuit may also be thromboresistant because albumin attaches to PVC, preventing fibrinogen adhesion to the PVC and thereby reducing platelet adhesion [73, 74]. A study of 200 children supported with the same bypass pump and oxygenator compared heparin coating with albumin coating of the circuit and failed to show a difference in measured cytokine levels (IL-6 and IL-8). [75]. These findings are consistent with an adult study comparing the effect of roller pump, centrifugal pump, uncoated, and heparin-coated surfaces on 73 patients and showing that CPB affects the cellular immune system independently of the type of CPB system. [76]

Ventricular assist devices
The advantages of VAD circuits over ECMO are reduced priming volume from the lack of an oxygenator and shorter tubing, and less trauma to blood cells. VADs are designed to reduce the work of either the left ventricle, right ventricle or both ventricles in situations of heart failure, and to restore adequate cardiac output. VAD circuits are composed of inflow and outflow cannulas, a pump (intracorporeal or paracorporeal), driving line power source, and a system controller (Figure 32.4) [77–82]. The inflow cannula attaches to the atrium or to the apex of the ventricle and transports blood from the left or right heart to the device. For left-sided VAD, the outflow cannula is connected to the ascending aorta; and in right-sided VAD, the outflow cannula connects to the pulmonary artery. With regard to the optimal placement of inflow cannulas, ventricular cannulas achieve better unloading of the heart, reducing wall stress, which allows better ventricular recovery, and they have a lower incidence of thrombosis. However, in patients with a small ventricular chamber, such as non-compaction cardiomyopathy, endocardial trabeculations can obstruct a ventricular inflow cannula. These patients may require left atrial cannulation or left ventricular cavity myectomy before ventricular cannulation [83].

The length of planned support is typically used to divide VADs into those for short-term use (typically < 2 weeks) and those for long-term use. (Table 32.1). They are also classified based on the mechanism that propels blood. Ejection can be achieved with a rotational device (e.g. centrifugal pumps), a pneumatic pusher plate (e.g. Berlin Heart), or via axial flow (e.g. HeartMate II®).

The available VAD systems for pediatric use in the United States are described below.

There are many manufacturers of centrifugal pumps, including Biomedicus Biopump, CentriMag, Rotaflow and Capiox® (Terumo, Ann Arbor, MI, USA) (Figure 32.3). These pumps convert mechanical energy from the motor to kinetic energy which drives blood by centrifugal forces [84]. At Texas Children’s Hospital we utilize the Rotaflow centrifugal pump because it has low priming volume (32 mL), surface area, and passage time, minimizing hemodilution and blood trauma [85] (Figure 32.5). It also has a reduced clotting potential due to the combination of mechanical and magnetic bearings, requiring less anticoagulation. This pump has the highest hydraulic efficiency of all commercially available pumps. As noted earlier, it can provide 10 L/min of pump flow rate against 400 mmHg of total head pressure, indicating high performance [86]. As with all rotary blood pumps, higher flow rates are achieved with lower pressure differentials across the pump. The Rotaflow can operate as a stand-alone console or be incorporated into the HL 20 heart–lung machine. It has its own battery backup and power supply. The main
Table 32.1 Ventricular assist device systems available in the United States

<table>
<thead>
<tr>
<th>Pump/flow type</th>
<th>Stroke volume (mL)/pump speed (rpm)</th>
<th>Flow range (L/min)</th>
<th>BSA range (m²)</th>
<th>Device type</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short term (&lt;14 days)</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Rotaflow®</td>
<td>Centrifugal/ non-pulsatile</td>
<td>0–4,500 rpm</td>
<td>0–9.99</td>
<td>No minimum&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>TandemHeart®</td>
<td>Centrifugal/ non-pulsatile</td>
<td>3,000–7,500 rpm</td>
<td>0–5&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&gt;1.3</td>
</tr>
<tr>
<td>Impella® 2.5</td>
<td>Centrifugal/ non-pulsatile</td>
<td>0 to 50,000</td>
<td>0–2.5</td>
<td>&gt;0.9 to 1.1&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Impella® 5</td>
<td>Centrifugal/ non-pulsatile</td>
<td>0 to 33,000</td>
<td>0–5</td>
<td>&gt;1.1&lt;sup&gt;c&lt;/sup&gt;</td>
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<tr>
<td><strong>Long term (&gt;14 days)</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Berlin Heart EXCOR®</td>
<td>Pulsatile</td>
<td>12, 15, 25, 30, 50, 60 and 80 mL</td>
<td>Variable&lt;sup&gt;d&lt;/sup&gt;</td>
<td>&gt;0.2</td>
</tr>
<tr>
<td>SynCardia Total Artificial Heart</td>
<td>Pulsatile</td>
<td>50 and 70 mL</td>
<td>Up to 9.5</td>
<td>&gt;1.7–2.5</td>
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<tr>
<td><strong>Continuous-flow ventricular assist devices</strong></td>
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<tr>
<td>HeartMate II</td>
<td>Axial</td>
<td>6,000–15,000 rpm</td>
<td>&gt;2.5</td>
<td>&gt;1.4</td>
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<tr>
<td>HeartWare®</td>
<td>Centrifugal/ non-pulsatile</td>
<td>1,800–4,000</td>
<td>0–10</td>
<td>&gt;1.4–2.6</td>
</tr>
</tbody>
</table>

See text for complete details.

<sup>a</sup>Smaller patient reported 1.9 kg neonate

<sup>b</sup>2. 5 L/min flow needs a 17 F arterial cannula; 4 L/min flow needs a 15 F arterial cannula.

<sup>c</sup>The Impella is a partial support device which enhances the patient cardiac output – the limitation is the vascular access needed for the size of the cannulas.

<sup>d</sup>Depends on pump size and set rate.

Figure 32.5 Rotaflow® centrifugal pump. See text for details.

The limitation of centrifugal pumps is the ability to provide prolonged support (>1 week) because of complications such as thrombosis, bleeding and/or infection [72–76,86]. However, a recent report describes 2 months of VAD support using the Rotaflow pump in an infant with dilated cardiomyopathy (DCM) [87].

The Tandem Heart®. (Cardiac Assist Inc., Pittsburgh, PA, USA) [88] (Figure 32.6) is a percutaneously inserted centrifugal pump used for short periods to support the left or right ventricle. For left ventricular support, the venous cannula is placed trans-septally in the left atrium and the arterial cannula is placed in the femoral artery percutaneously, or by surgical cutdown in smaller patients. Use in pediatrics is limited by the cannula sizes, 21 French venous and 15–17 French arterial cannula [89–91]. The electromechanical controller system has a simple graphical user interface. This device was initially applied during high-risk coronary revascularization procedures in adults. It has been used in children to support the failing right ventricle of a patient with single-ventricle physiology and for right ventricular dysfunction after heart transplantation [92]. The smallest patient reported in this case series weighed 38 kg. Recently the Tandem Heart has been described for use as part of a percutaneous strategy of biventricular support, inserting the Tandem Heart to support the right ventricle and the Impella as an LVAD [93].

Impella®. (Abiomed, Danvers, MA, USA) [94] (Figure 32.7) is a relatively new microaxial flow device with two different pump sizes, at 2.5 and 5 L/min [91]. The smaller pump is designed for use in adults requiring partial left ventricle support during high-risk cardiac catheterizations, such as ablation procedures and urgent catheterizations for acute coronary syndromes, but this
smaller pump can also provide full left ventricle support in pediatric patients. The Impella® 5 L/min provides full left ventricle mechanical support for adults where it has been used as a bridge to recovery and a bridge to a permanent support device. The Impella is inserted retrograde through a femoral artery, with the device inlet zone resting in the left ventricle cavity where blood is collected and propelled into the aorta. The deployment is performed under direct vision by fluoroscopy and transesophageal echocardiography (TEE). Like many devices initially designed for use in adults, the Impella will have limited use in smaller patients because of its size. The 2.5 L/min pump is 4 mm in diameter and requires a 9 Fr sheath for delivery, and the 5.0 L/min pump is 7 mm in diameter, requiring a femoral cutdown for delivery. It has been placed in smaller patients via a sternotomy into the ascending aorta [95].

The automated controller delivers three different functions: it provides an interface to monitor flow; there is a catheter fluid purge function; and it has internal backup power for up to 60 minutes. The pediatric experience...
is limited to small case series, and the smallest patient supported was 10 years old, weighing 21 kg with a body surface area (BSA) of 0.93 m² [95].

The Berlin Heart VAD (EXCOR®). [96] (Figure 32.8) is a pulsatile, paracorporeal device that is suitable for all pediatric patients, including neonates. It is available in several sizes (10–60 mL). The smallest pumps are appropriate to support neonates and infants (weight 3–8 kg) and the 25 and 30 mL pumps will support children weighing up to 20–25 kg. It provides pulsatile flow delivered through a pneumatically driven thin membrane pump. In diastole, blood enters the pusher-plate polyurethane chamber through an inlet valve, and enough negative pressure is generated to aid in pump filling. In systole the blood-filled chamber is compressed from an air-filled chamber, creating pulsatile systolic flow ejected through the outlet valve to the aorta. Mechanical valves direct the flow, and there is no direct contact between the pumping mechanical parts and blood. The maximum systolic positive pressure generated is 350 mmHg and the maximum negative driving pressure is −100 mmHg. High pressures are sometimes needed to overcome the resistance of small pediatric cannulas. The pump rate can be adjusted to between 30 and 150 beats/min and the systolic time can be adjusted to between 20 and 70% of the cycle; these parameters can all be monitored and adjusted on the external driving unit. The blood pump is transparent, allowing visual inspection of filling, emptying and thrombus formation. If thrombus formation in the pump or cannulas is found, the pump should be exchanged to avoid systemic embolization. The blood-contacting surfaces of the pump, including the polyurethane valves, are covered with Carmetex® bioactive heparin coating for prevention of thromboembolic complications. The EXCOR® has silicon cannulas with a Dacron covering that works as a biologic barrier against ascending infections.

Patients supported with this device often do not require mechanical ventilation; they can eat normally and ambulate, making ICU discharge possible [97,98]. The EXCOR® can be used for biventricular support using two pumps (right VAD [RVAD] and LVAD) controlled by the same external driving unit. The one prospective trial from the USA comparing the EXCOR® with ECMO as a bridge to transplantation showed better survival rates with the VAD than with ECMO in two different BSA cohorts (cohort 1, < 0.7 m²; cohort 2, 0.7 to < 1.5 m²). Unfortunately the incidence of serious adverse events was high in
both groups, including major bleeding (42% and 50%, respectively), infection (63% and 50%, respectively), and stroke (29% and 29%, respectively). In addition, the need for pump exchanges due to thrombosis was frequent. The higher-risk patients in the US pediatric experience had smaller size, renal dysfunction, hepatic dysfunction, and required biventricular assist. ECMO before implantation and CHD were not associated with worse outcome in this study population [99,100].

The **HeartMate II**. (HM II) (Thoratec Corp., Pleasanton, California, USA) [101] (Figure 32.9) is an axial-flow VAD, which uses an electrical motor accelerating the blades of a rotating impeller to propel blood that enters the device. It is a smaller and simpler device with only one moving component and without unidirectional valves, and is implanted intracorporeally for patients with a BSA > 1.4 m² [102]. Continuous-flow devices have a significantly lower incidence of complications and overall mortality. The HM II has been compared with two pneumatic VADs, the HeartMate XVE LVAD (HMXVE) and the Thoratec Implantable VAD (Thoratec Corporation) as a bridge to transplant in adults [103]. The survival of patients remaining on support at 1 year was 85% for HM II group vs. 70% for the comparison group. In addition, the HM II has been used in adults with advanced heart failure as destination therapy. In a prospective, randomized clinical trial comparing the HMII and the HMXVE LVAD, a significant improvement in survival and an overall reduction in adverse events was observed with the HMII [104,105]. The experience of using a VAD for destination therapy in the pediatric population is limited and it has been used only in patients with a short life expectancy [106].

**The HeartWare Ventricular Assist System®.** (HVAD) (HeartWare, Inc., Miami Lakes, FL) [107] (Figure 32.10) is a small intrapericardial centrifugal flow pump with a rotating impeller, forcing blood through the device using hydrodynamic and centrifugal forces. The displacement volume is 50 mL and is capable of flowing up to 10 L/min. The inflow cannula is integrated within the device and is inserted into the left ventricle by an adjustable sewing ring. The 10 mm outflow graft is anastomosed to the ascending aorta [108]. An external console controls the pump, regulates power, monitors performance, and displays alarms. The pump is connected to the console by a subcutaneous driveline through patient’s abdominal wall. For safety reasons, the HVAD is powered by two of three different sources: rechargeable lithium batteries, alternating current (AC) power, or a 12 V DC power source. Good survival rates were reported for the first 50 adult patients supported with HVAD: 90% at 6 months, 84% at 12 months, and 79% at 24 months [109]. One small pediatric series has been reported where seven patients were managed successfully, six transplanted and one remained on the device for 136 days awaiting transplantation at the time of the publication [110].

**SynCardia Total Artificial Heart (STAH).** (SynCardia Systems Inc., Tucson, Ariz) [111] (Figure 32.11) is a pneumatically driven pulsatile device designed with two
prosthetic polyurethane ventricles (70 mL) that provide biventricular support. Each ventricle has two mechanical valves providing unidirectional inflow and outflow from the ventricle. The valves are single-leaflet Medtronic-Hall (Minneapolis, MN) size 27 mm for the inlet and 25 mm for the outlet. The STAH has the largest inflow and shortest distance of blood traveled of all available VADs. The large valves and short blood path provide very little resistance, thereby decreasing stasis and thrombosis [112,113]. The prosthetic ventricles are coupled with silicone cuffs to two atrial connectors and two connectors on the end of the grafts sewn to the aorta and pulmonary artery. The external console displays the pressure waveform of each cardiac cycle and has two independent controllers for emergency backup. The STAH is powered by compressed air delivered by two separate wire-reinforced conduits connected to the right and left prosthetic ventricles. This device is indicated for patients who are unable to be supported by VAD, such as those who require biventricular support and/or have pulmonary hypertension (>4.5 Wood units). STAH has been used successfully after catastrophic intraoperative heart damage, severe aortic valve insufficiency, failing Fontan, refractory arrhythmias, or irreversible cardiac rejection after transplantation. As with other devices designed for adult use, the pediatric use is limited because the device needs a distance between the sternum and the 10th anterior vertebral body of >10 cm. The recommended BSA is >1.7 m² but it has been used successfully in patients with a BSA of between 1.5 to 1.7 m². Currently the company is developing a smaller pump (50 ml), which would be suitable for patients with a BSA of between 1.2 and 1.79 m². Copeland et al. reviewed the first 101 adult patients managed with STAH as a bridge to transplant with a mean support time of 87 days (range 1–441) and overall survival to transplant of 68.3%. The adverse events included strokes in 7.9% and the need to take-back for hemorrhage in 24.7% of cases [114]. In this series only nine patients had a BSA <1.7 m².

**KEY POINTS: DEVICES**

- Roller pumps produce a linear increase in hemolysis that is not observed with centrifugal pumps.
- Centrifugal pumps are generally used for short-term ventricular support (less than 2 weeks)
- The Berlin Heart EXCOR® device:
  - has several sizes of pumping chambers that allow it to be used in 3 kg infants to adult-sized patients;
  - allows patients to be extubated, ambulate and eat normally;
  - can be used as an LVAD, RVAD or BiVAD;
  - is used for long-term circulatory support (months).

**Role of echocardiography in mechanical support**

**Extracorporeal membrane oxygenation**

Transthoracic echocardiography (TTE) and/or TEE are useful in detecting complications before cannulation, during cannulation, and while weaning from ECMO [115]. Before initiating ECMO, TTE is used to detect reversible causes of cardiogenic shock such as cardiac tamponade or severe valvular insufficiency (e.g. aortic regurgitation), or to detect anatomic variations that affect cannula insertion in the right atrium, such as a prominent Chiari network or an aneurysmal atrial septum. If central cannulation through sternotomy is required, TEE is a better choice, as most TTE windows are not available. Kuenzler et al. analyzed 193 pediatric patients supported with ECMO, detecting a 17.8% incidence of cannula malposition that was reduced to 3.3% with the use of echocardiography [116]. After the initiation of ECMO, echocardiography is used to assess left ventricular unloading and the potential need for left atrial venting via surgical or balloon atrial septostomy [117]. Echocardiography is also used to monitor aortic valve opening, because limited aortic ejection increases the risk of blood stasis, leading to thrombosis. Increasing aortic valve opening during ejection is an indication of left ventricular recovery when the flow through the ECMO circuit is reduced. During ECMO support, echocardiography is used to periodically evaluate cannula positioning and thrombi formation, chamber filling and function, and cardiac compression from pericardial effusion. Tamponade physiology is typically not evident until the patient is weaned from ECMO [118].
Ventricular assist devices
The American College of Cardiology, AHA and American Society of Echocardiography consider TEE to be a class 1 indication for the insertion of a VAD (Table 32.2) [118–122]. Before the initiation of VAD support, TEE is useful to rule out conditions that jeopardize VAD function, such as mitral stenosis, endocardial trabeculations that may limit filling of the device, and aortic insufficiency, which will reduce cardiac output and impede left ventricular unloading (Figure 32.12A,B). Mitral regurgitation and aortic stenosis do not affect device function. Mitral regurgitation generally improves from left ventricular unloading with an associated reduction in left ventricle chamber size and mitral annulus size. Preoperative echocardiography should screen for septal defects, and unrepaird atrial or ventricular communications should be closed before VAD insertion, because unloading of the left-sided chambers allows desaturated venous blood to cross to the systemic circulation and will produce significant oxygen desaturation (Figure 32.12C). Echocardiography will also screen for potential intracardiac thrombi, as thromboembolic events are common and potentially devastating. Before placing an LVAD, the right heart size, function and tricuspid valve regurgitation should be assessed to determine if biventricular support is indicated. Echocardiographic parameters that indicate higher risk of right ventricular failure in adult patients have been established [123,124]. As right ventricular function commonly has significant improvement from unloading the left ventricle in children, real-time visualization of right ventricular function should be performed by intraoperative TEE as LVAD support is initiated [125].

Devices that are placed with the use of CPB should undergo interrogation of the inflow and outflow cannulas before weaning. The inflow should be laminar with a velocity < 2 m/s. A peak flow velocity > 2.3 m/s along with turbulent flow is indicative of inflow cannula obstruction and an indication for surgical revision (Figure 32.13). Normal outflow has a low-velocity (peak velocity 1.0–2.0 m/s) (Figure 32.14). Continuous monitoring right ventricular function and the detection of air is crucial for early intervention. Air may enter through suture lines if the left ventricle completely collapses and sub-atmospheric intra-device pressures develops. While weaning from CPB echocardiography is used to determine right ventricular function, and to guide (RVAD) implantation, if needed (Figure 32.15). Severe septal shifting to the left is an indicator of right-sided heart failure and the need for RVAD. A temporary RVAD can sometimes be used when rapid right ventricular recovery is anticipated. Once LVAD support is started and CPB flows are decreased, TEE is used to quantify left ventricle decompression along with the degree and direction of movement of the interventricular septum. When continuous-flow devices are used, TEE is used to monitor interventricular septum shift, sufficient left ventricular unloading, and ensure that the aortic valve opens periodically. The aorta should be carefully scanned to rule out the possibility of dissection distal to the outlet cannula insertion site. Finally, after chest closure, a final scan is performed to exclude the possibility of kinking of the cannulas or right ventricular compression.

Transeosophageal echocardiography is also useful to guide the percutaneous VAD placement of the Tandem Heart and Impella assist devices. TEE can guide the Tandem Heart atrial trans-septal cannulation through the fossa ovalis. If the inflow cannula moves into the right atrium, this is easily identified by TEE and from arterial desaturation (Figure 32.16). TEE imaging of the needle tip is important to avoid puncture of the aorta or atrial wall [126]. Echocardiography imaging of the STAH is technically difficult due to echocardiographic brightness of the device and its valves. TEE is still used to diagnose right-to-left shunting, distortion, and compression of systemic and pulmonary venous return to the native atrium, all of which affect STAH function. TEE also guides the de-airing procedures by imaging the ascending aorta. Once the device is functioning, the Medtronic-Hall valves (tilting disc) in the ativoventricular position can be interrogated to assure adequate function [127].

Weaning from circulatory support
ECMO weaning
Patients are weaned from ECMO when their cardiac function recovers and their lungs can support adequate oxygenation and ventilation using traditional mechanical ventilation. When the myocardium has an acute insult, such as acute myocarditis or ischemia from a prolonged period of CPB, ECMO can usually be weaned 72 hours after the initiation of support. Echocardiographic criteria associated with successful ECMO weaning include left ventricular ejection fraction > 35%, left ventricular outflow tract velocity–time integral > 10 cm, lack of ventricular dilatation, and no pericardial effusion [128]. In anticipation of ECMO weaning, inotropic support and ventilation are optimized, followed by a gradual reduction in the ECMO flow while carefully evaluating the patient’s hemodynamics (heart rate, blood pressure, arterial waveform, SpO₂, central venous pressure, and pulmonary artery pressure). Tissue perfusion is evaluated with serum lactate levels and cerebral/somatic oximetry trends. Once flow rates are reduced to 25% of full support, a connection (bridge) between the arterial and venous cannulas is opened to allow blood to recirculate in the ECMO circuit and avoid thrombosis. If the cardiac function is marginal after weaning from ECMO, the chest is not closed until cardiac and pulmonary function recovers [128]. Prolonged cardiac ECMO support (>14 days) and failure to wean from ECMO is associated with high mortality [129,130], and potential transplant candidates should therefore be transitioned to a VAD when their lung function has recovered and pulmonary hypertension is controlled.
<table>
<thead>
<tr>
<th>TEE windows</th>
<th>Comments</th>
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<td>Pre-bypass phase</td>
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<tr>
<td>Monitor:</td>
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<tr>
<td>LV size, filling and function</td>
<td>ME4Ch, TG SAX, TG 2ch</td>
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<tr>
<td>RV size, filling and function</td>
<td>ME4Ch, MERVIO</td>
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<td>Endocardial trabeculations (non-compaction cardiomyopathy)</td>
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<td>Decompression of LV and LA</td>
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<td>Air entrainment</td>
<td>ME4Ch, MELAX</td>
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</tbody>
</table>

LV, left ventricle; ME4Ch, mid esophageal four chamber; TGSAX, transgastric short axis; RV, right ventricle; MERVIO, mid-esophageal right ventricle inflow/outflow tract; LVEDD, left ventricular maximal end-diastolic diameter; RVEDD, RV maximal end-diastolic diameter; PFO, patent foramen ovale; ASD, atrial septal defect; VSD, ventricular septal defect; RVAD, right ventricular assist device; MEBc, mid-esophageal bicaval; DTGSCh, deep transgastric five chamber; DALAX, descending aorta long axis; LVAD, left ventricular assist device; TGLAX, transgastric long axis; MEmodBC, mid-esophageal modified bicaval; TVR, tricuspid valve repair; PASP, pulmonary artery systolic pressure; VpeakTR^2, peak velocity of the tricuspid regurgitant jet; CVP, central venous pressure; CWD, continuous wave Doppler; TR, tricuspid regurgitation.
Figure 32.12 Valvular and non-valvular conditions that affect ventricular assist device (VAD) function detected by transesophageal echocardiography. (A) Mitral stenosis limits the device filling by decreasing the inflow to the VAD. (B) Aortic insufficiency results in continuous backflow to the left ventricle (LV), decreasing forward output and hindering unloading of the heart. (C) Patent foramen ovale demonstrating a left-to-right shunt; with initiation of VAD support, LV pressure decreases, resulting in right-to-left shunt and causing arterial desaturation. AO, aorta; RA, right atrium; LA, left atrium; RV, right ventricle.

VADs: weaning from CPB to VAD
Intracardiac air is commonly seen during LVAD placement, and infield CO₂ insufflation is sometime used to reduce air emboli. Air can be trapped in the cannulas or the device itself and will be dislodged into the heart once blood starts to flow through the device. Air can have devastating effects if it reaches the coronary or cerebral circulation. As the right coronary sinus is the most anterior, it is the most common site for air emboli and will worsen right ventricular function. Continuous electrocardiogram with ST monitoring and TEE are mandatory while on CPB after ventilation is resumed. De-airing is achieved by placing the patient in the Trendelenburg position, increasing the mean arterial pressure, and using an aortic vent until all air is removed [131]. Successful weaning of CPB is achieved by reducing CPB flows while increasing the LVAD flows and using TEE surveillance of the right ventricular function, left ventricular volume, and the interventricular septal position. To optimize right ventricular function, milrinone, nitroglycerin, and/or prostaglandin E₁ are often used, inhaled nitric oxide is administered to reduce right ventricular function afterload, and ventilation is optimized. As the ventricles are in series, the output of one ventricle is the input of the other. With LVAD support, the left ventricular output increases, thereby increasing right ventricular function preload. The right ventricular function output depends on the relationship between the right ventricular function compliance, the septal shift, and right ventricular function afterload. Ideally one observes improved right ventricular function after the left ventricle is supported and the pulmonary capillary pressure decreases [132,133]. Table 32.3 shows the hemodynamic
changes and interventions with the two most common long-term pediatric MCS devices in the US.

**VADs: weaning from VAD to recovery**
Unloading the failing LV with a VAD can lead to reverse remodeling of the heart, decreased neurohormonal and cytokine activation, and normalization of cytoskeletal integrity of the ventricle. The reverse remodeling process has been described in patients with DCM. While the left heart is supported, medical treatment for heart failure should be optimized with angiotensin-converting enzyme inhibitors, β-blockers (preferably carvedilol) and aldosterone antagonist. Also patients should undergo extensive physical therapy and nutritional support to maintain and improve their strength. The criteria used for myocardial recovery and candidacy for LVAD explantation are sinus rhythm, lack of or trace mitral regurgitation, left ventricular ejection fraction ≥ 45%, and left ventricular end-diastolic diameter ≤ 1 standard deviation below mean for age (≤55 mm for adult-sized patients) along with serum brain natriuretic peptide (BNP) < 100 pg/mL. In a report including both pediatric and adult patients with DCM, 8.8% of patients could be weaned to recovery. In this study, patients were more likely to be weaned to recovery if they were younger and/or had a pulsatile VAD [134]. There are several case reports or case series of children recovering from acute myocarditis after VAD support [135–137].

**Anesthesia, analgesia, and sedation for mechanical support**
Patients who require ECMO or VAD support due to failure to wean from CPB have been under general anesthesia for the surgical procedure and this should continue during insertion of the MCS system. In addition, plans for continued sedation and analgesia should be made in order to smooth the transition of care in the ICU. Patients requiring ECMO in the ICU are already intubated, have invasive pressure monitoring, and are receiving infusions for sedation and analgesia. If a patient requires the airway securing before initiation of ECMO, the surgical team should be immediately available in preparation of circulatory collapse after the induction of anesthesia. There are specific pharmacological considerations when anesthetizing children receiving mechanical support of the circulation.

**Drug disposition changes on mechanical support**
In addition to the usual reasons why critically ill patients have poorly predictable drug pharmacokinetics, such as
altered hepatorenal perfusion and function, drug interactions, reduced protein binding, and renal replacement therapy, the patient on ECMO will have additional pharmacokinetic changes related to the volume of the circuit, the polymer components, and the altered perfusion and drug elimination.

On initiation of ECMO, the fluid in the membrane oxygenator and tubing adds 200–300 mL to the circulating volume, depending on the circuit. The effect of this is relatively insignificant for drugs with a high volume of distribution ($V_d$), such as fentanyl, which show relatively little change in plasma concentration, as, following ECMO initiation, drugs will diffuse back into the plasma from the tissues. Drugs with lower $V_d$, such as gentamicin, vancomycin, and non-depolarizing neuromuscular blockers, would be expected to have a relatively larger change in plasma concentration and may prolong the elimination half-life [138]. In these cases, a higher loading dose is required, but the dosing interval would need to be increased. The hemodilution of ECMO may also be associated with a reduction in plasma protein concentration, which in turn would increase the free fraction of highly protein-bound drugs like teicoplanin or ceftriaxone. This will cause a transient increase in clinical effect, but there will also be an increase in diffusion of drug to the tissues and hence a reduction in plasma concentration. The addition of albumin to the pump circuit will reduce this effect.

In addition to the effects of hemodilution, a significant amount of drug adsorption can occur on the large surface area of tubing or the membrane oxygenator of the ECMO circuit, further increasing the apparent $V_d$ of drugs. The opposite may occur when a drug is ceased, whereby sequestered drug may be released back into the circulation, which adds further unpredictability of drug disposition and may prolong the drug’s effect [139]. The degree of this sequestration depends on both the materials used in the ECLS circuit and the nature of the drug. ECLS tubing is made of PVC and the membranes may comprise several biomaterials, including silicone rubber, polypropylene, polymethylpentene (PMP) or PVC [140]. In general, drugs are more likely to adhere to the PVC if they are highly lipophilic, such as opioids, propofol, and benzodiazepines. In vitro studies show that morphine has less adsorption from PVC than fentanyl, 40% for morphine vs. 86% for fentanyl [141]. Most of this adsorption is onto the tubing itself rather than the membrane oxygenators, although newer modified surface-coated PVC tubing still sequesters approximately 40% of fentanyl and 35–58% of morphine [141].

Multiple factors in a heterogeneous patient population make accurate prediction of drug doses extremely difficult. Appreciation of the issues help the clinician to make sensible drug management decisions, particularly when initiating ECLS and changing the circuit. Appropriate sedative and analgesic dosing can be difficult, running the risks associated with under-and over-sedation. Under-sedation is associated with pain, ventilator dyssynchrony and inadvertent line removal, whereas oversedation is associated with prolonged ventilation and hospital-acquired infections. Vigilant clinical monitoring is therefore mandatory. Prolonged analgesic infusions with both fentanyl and morphine are associated with tolerance; however, the long duration of action makes morphine the preferred analgesic. As always, careful drug monitoring should be employed where possible (e.g. gentamicin), in order to guide dosing regimens.

### KEY POINTS: ANESTHESIA AND ANALGESIA FOR MECHANICAL SUPPORT

- Pharmocokinetics of medications can be significantly altered by ECMO or VAD.
- $V_d$ is increased, and drugs with low $V_d$ such as non-depolarizing neuromuscular blockers will have a lower concentration and require a higher loading dose.
- Hemodilution may reduce plasma proteins, which would increase the free fraction of highly protein-bound drugs.
Figure 32.15 (A) Mid-esophageal four-chamber view pre-cardiopulmonary bypass (CPB) showing biventricular dilation in a toddler with dilated cardiomyopathy. (B) Mid-esophageal four-chamber view pre-CPB with color Doppler showing a severe eccentric tricuspid regurgitant jet directed towards the interventricular septum. (C) Mid-esophageal four-chamber view post-CPB while the patient is on a biventricular assist device. Note the decompression of both the right and left ventricles and the inflow cannulas (arrows). Observe the right ventricular assist device inflow cannula in the right atrium (RA) and the left ventricular assist device inflow cannula in the left ventricle (LV). RV, right ventricle; LA, left atrium.

Figure 32.16 (A) Mid-esophageal aortic short-axis view illustrating the Tandem Heart inflow cannula in the left atrium (LA) (arrow). (B) Mid-esophageal aortic short-axis view after transporting the patient to the intensive care unit – severe desaturation was noticed. Observe the Tandem Heart inflow cannula in the right atrium (RA) (arrow). RV, right ventricle; Ao, aorta.

• Lipophilic medications such as opioids, benzodiazepines, and propofol will bind to the circuit with the following consequences:
  - Lower plasma levels are seen when initiating the medication.
  - There may be continued release of the medication from the circuit after the drug is discontinued.

Anticoagulation, antifibrinolytics, and platelet anti-aggregation therapies

The exposure of blood to the ECMO circuit causes cellular activation of complement, coagulation, fibrinolysis, and inflammation and these effects are more pronounced in neonates and infants because of their lower blood volume relative to the circuit size [142]. Anticoagulation is mandatory when initiating ECMO and it is challenging to achieve adequate anticoagulation without producing hemorrhagic complications. Unfractionated heparin is the first-line drug to achieve anticoagulation on ECMO. Heparin binds to antithrombin III (ATIII), producing anticoagulation by inhibition of activated factors Xa, IXa, XIa, XIIa, and, to a lesser extent, IIa (thrombin). Adequate levels of ATIII are required, and therefore plasma, which contains ATIII, is often added to the circuit prime. The anticoagulation effect of heparin is most commonly monitored by the activated clotting time (ACT), a real-time bedside test that measures whole blood clotting (platelets, red cells, and clotting factors) after exposing the blood to activators (kaolin or...
Table 32.3 Management of perioperative hemodynamic changes during mechanical support

<table>
<thead>
<tr>
<th>Device</th>
<th>Hemodynamic change</th>
<th>Possible etiology</th>
<th>Device inspection and possible intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berlin Heart EXCOR®</td>
<td>Hypotension</td>
<td>Hypovolemia</td>
<td>Inspect chamber (reflective mirror) for wrinkling in diastole</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Fluid bolus (10 mL/kg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Increasing device rate not recommended as it will shorten fill time</td>
</tr>
<tr>
<td></td>
<td>Hypotension</td>
<td>Systemic vasodilation (e.g., with induction of anesthesia)</td>
<td>Chamber may be filling fully</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Alpha agonists (phenylephrine, norepinephrine) or vasopressin</td>
</tr>
<tr>
<td>HeartMate II</td>
<td>Hypotension</td>
<td>Hypovolemia</td>
<td>↓↓ device flow (lowest 3 L/min) and ↓ rpm (lowest 8,000)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Fluid bolus</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Increasing device rpm is not recommended as it will shorten the fill time</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td>Pain</td>
<td>↑ device flow with ↔ in rpm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Awareness under anesthesia</td>
<td>Alpha agonists (phenylephrine, norepinephrine) or vasopressin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anxiety</td>
<td>↑ device flow with ↔ in rpm</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sedatives, analgesics</td>
</tr>
</tbody>
</table>

† mild increase; ††, significant increase; †, mild decrease; †††, significant decrease; ↔, no change.

celite). The ACT does not correlate well with activated partial thromboplastin time (aPTT) and/or antifactor Xa in heparinized neonates receiving ECMO [143]. ACT can be prolonged or shortened in the absence of heparin in patients on ECMO. Elevated D-dimers, low platelet count or platelet dysfunction, low fibrinogen, hypothermia, and/or hemodilution can prolong ACT. Alternatively, ACT can be shortened in hypercoagulable states, making the dosing of heparin faulty and putting the patients at risk for under-dosing (thrombosis) or over-dosing (bleeding).

More accurate monitoring of coagulation is provided from aPTT and/or antifactor Xa, but these are not bedside tests. Antifactor Xa levels exclusively measure the heparin effect on ATIII by measuring the inhibition of factor X conversion. On the other hand, the aPTT measures the activity of both the intrinsic and common pathways of the coagulation (factor XII, XI, X, IX, VIII, V, II and fibrinogen [factor I], prekallikrein, high-molecular-weight kininogen factors). Heparin infusions are titrated to antifactor Xa levels of 0.3–0.7 IU/mL or aPTTs of 1.5–2.5 times the normal value [143–145]. The anticoagulation strategy used at Texas Children’s Hospital includes a heparin bolus dose of 100 U/kg to achieve an ACT of 180–200 seconds at the initiation of ECMO, followed by an infusion of 8 U/kg/hour (range 6–60 U/kg/hour), and adding heparin to the pump prime. Neonates have a higher heparin need secondary to faster heparin clearance and volume of distribution (higher water content). During ECMO, the primary source of heparin clearance is through inactivation in the circuit. Platelets are transfused to keep platelet count > 100,000/mm³ and cryoprecipitate is administered when fibrinogen is below 150 mg/dL. If platelets are administered into the ECMO circuit, they should be infused distal to the oxygenator to avoid damage. In patients with heparin-induced thrombocytopenia, direct thrombin inhibitors have been used in pediatric ECMO [146]. Selected use of factor VII has been reported in refractory bleeding on ECMO, but it has also been associated with life-threatening thrombosis [147]. Thromboelastography is an important tool in the decision-making, because it provides information on all aspects of coagulation and fibrinolysis (Table 32.4) [148].

A percutaneously placed VAD, like the Tandem Heart, only requires partial anticoagulation with heparin, targeting an ACT > 180 seconds. Most long-term VADs

Table 32.4 Treatment protocol for citrated thromboelastogram (TEG)

<table>
<thead>
<tr>
<th>TEG value</th>
<th>Clinical cause</th>
<th>Suggested treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>R &gt; 14 min</td>
<td>↓ clotting factors</td>
<td>FFP 4 mL/kg</td>
</tr>
<tr>
<td>R &gt; 18 min</td>
<td>↓↓ clotting factors</td>
<td>FFP 8 mL/kg</td>
</tr>
<tr>
<td>MA &lt; 46</td>
<td>↓ platelet function</td>
<td>Platelets 1 unit/5 kg</td>
</tr>
<tr>
<td>Angle &lt; 55°</td>
<td>↓ fibrinogen level</td>
<td>Cryoprecipitate 0.6 U/kg</td>
</tr>
</tbody>
</table>

R, time from when the sample is put on the TEG until the first significant levels of detectable clot formation; MA, maximum amplitude; FFP, fresh frozen plasma; TEG, thromboelastography; †, mild decrease; ††, significant decrease.
are placed while the patient is on CPB and under full anticoagulation and commonly the heparin is reversed with protamine chloride once the VAD is initiated. In the first 24 hours after VAD placement, there is a high incidence of reoperation to achieve hemostasis. To decrease the risk of postoperative bleeding, antifibrinolytics such as aminocaproic acid or tranexamic acid are often used, even though there are no specific studies in pediatric VAD implantations. After the immediate postoperative period, the risk of bleeding decreases while the risk of thrombosis increases, and heparin is used at doses of 3–20 U/kg/hour to target an aPTT of 1.5 times normal. The ATIII levels should be checked and kept above 70% to avoid thrombotic complications. Currently, most of the institutions follow the Edmonton antithrombotic protocol once the patient is discharged from the ICU. This protocol involves a three-drug regimen: aspirin, dipyridamole, and either warfarin (≥12 months) or enoxaparin (<12 months) [10]. Platelet aggregation studies are used to follow the platelet function and guide the administration of aspirin and dipyridamole. Infection will increase the risk of clotting, and anticoagulation monitoring should increase in frequency when infection is suspected.

**Anti-infective therapy**

Extracorporeal membrane oxygenation patients with an open sternum and those who required emergent cannulation are at greater risk of developing a nosocomial infection, and antibiotic prophylaxis is recommended [149]. Many antibiotics adhere to the biomaterials of the ECMO circuit, decreasing their bioavailability, and require re-dosing after circuit changes. First- or second-generation cephalosporins are a reasonable option for prophylaxis in populations that do not have a high incidence of methicillin-resistant *Staphylococcus aureus* (MRSA) [150,151].

There is wide variability in the prophylactic antibiotics regimens used in patients supported with VAD, ranging from one-drug to four-drug regimens including fluconazole [152]. Most centers use a beta-lactam antibiotic used with vancomycin if the risk of MRSA is high [153]. Prophylaxis should start before device placement and be continued in the immediate postoperative period.

VAD bloodstream infections can usually be controlled with adequate intravenous therapy, but intracorporeal infections usually require surgical debridement, drainage of infected fluids, and device replacement.

**Outcomes and complications of extracorporeal support**

The number of patients in all age ranges (neonatal, infant, pediatric, and adult) requiring ECLS for cardiac disease has increased rapidly in the last 10 years. The ECMO survival to hospital discharge in children with heart disease is 40–45%, which is lower than the survival rate in children with respiratory disease [6,23]. Although most of the outcome data are based on the ELSO registry, which has collected over 50,000 patients since 1984, information about outcome other than survival, such as cardiorespiratory function, neurodevelopmental outcomes, and quality of life, are not collected by ELSO [23]. In addition, until 2013 there was no severity of illness scoring within the registry, so certain data have so far been difficult to interpret; for example, venoarterial ECMO for neonates with respiratory failure has a mortality of 29%, but with veno-venous ECMO, the mortality is 16%. Without knowing the illness severity, we cannot ascertain what impact the mode of ECLS has on these figures [6].

Critically ill patients requiring central or peripheral mechanical support are at risk of serious complications, most of them related to organ hypoperfusion, bleeding, coagulopathy, systemic inflammatory response, embolic events (air or thrombus), hemolysis, and sepsis. The design of the mechanical support carries inherent risk; oxygenators run the risk of red cell damage and the tubing and multiple connectors carry a risk of clot formation and gas embolization. The frequencies of mechanical and patient-related complications are summarized in Tables 32.5 and 32.6. We see that overall mechanical failure is relatively uncommon but is associated with a significant mortality. Of the patient-related complications, bleeding from cannula and surgical sites remains a significant risk that carries a high mortality. There is a paucity of data on the long-term consequences of ICH.

**ECMO for cardiac support**

Cardiac failure and sequelae of low cardiac output are the most common causes of mortality after ECMO for cardiac reasons [9]. For post-cardiotomy patients, outcomes vary due to a variation in indication and deployment techniques [16]. In these patients, if an arterial pulsatile waveform is not seen after 72 hours of ECMO or VAD support, the prognosis is very poor and transplantation or withdrawal is considered [9,154]. Other prognostic indicators for ECMO, but not VAD, include urine output, renal function and pH at 24 hours [154]. In order to minimize poor outcome, mechanical support should be considered early to avoid prolonged LCOS and impaired organ perfusion. The prognosis for ECMO due to myocarditis is considerably better in all age groups compared with post-cardiotomy patients [6]; the natural history for myocardial recovery is different in this group and recovery can take anywhere from days up to years. It is recommended that these patients be transitioned to VAD from ECMO if there are no signs of recovery after 2 weeks [62]. For children requiring ECMO for cardiomyopathy there is a 57–61% survival rate [6], and new VAD technology appears to reduce transplant waiting list mortality compared with long-term ECMO support [34].
### Table 32.5 Mechanical complications of extracorporeal life support

<table>
<thead>
<tr>
<th>Complication</th>
<th>Age group</th>
<th>Cohort</th>
<th>Number of cases (%)</th>
<th>Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygenator failure</td>
<td>Neonatal</td>
<td>Respiratory</td>
<td>1,529 (6%)</td>
<td>53%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cardiac</td>
<td>368 (7.6%)</td>
<td>24%</td>
</tr>
<tr>
<td></td>
<td>Pediatric</td>
<td>Respiratory</td>
<td>681 (12.9%)</td>
<td>43%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cardiac</td>
<td>509 (8.8%)</td>
<td>35%</td>
</tr>
<tr>
<td>Tubing rupture</td>
<td>Neonatal</td>
<td>Respiratory</td>
<td>238 (0.9%)</td>
<td>66%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cardiac</td>
<td>42 (0.8%)</td>
<td>24%</td>
</tr>
<tr>
<td></td>
<td>Pediatric</td>
<td>Respiratory</td>
<td>161 (3%)</td>
<td>47%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cardiac</td>
<td>94 (1.6%)</td>
<td>37%</td>
</tr>
<tr>
<td>Pump malfunction</td>
<td>Neonatal</td>
<td>Respiratory</td>
<td>439 (1.7%)</td>
<td>66%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cardiac</td>
<td>80 (1.6%)</td>
<td>28%</td>
</tr>
<tr>
<td></td>
<td>Pediatric</td>
<td>Respiratory</td>
<td>132 (2.5%)</td>
<td>47%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cardiac</td>
<td>127 (2.1%)</td>
<td>42%</td>
</tr>
<tr>
<td>Cannula problems</td>
<td>Neonatal</td>
<td>Respiratory</td>
<td>2,978 (11.6%)</td>
<td>67%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cardiac</td>
<td>300 (6.2%)</td>
<td>34%</td>
</tr>
<tr>
<td></td>
<td>Pediatric</td>
<td>Respiratory</td>
<td>814 (15.4%)</td>
<td>51%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cardiac</td>
<td>350 (6%)</td>
<td>41%</td>
</tr>
</tbody>
</table>

Mechanical related complications of extracorporeal life support (ECLS) divided into age group and cohort. Pediatric refers to age range 1 month–16 years. Respiratory cohort refers to those with a respiratory indication for ECLS. Cardiac cohort refers to those with a cardiovascular indication for ECLS. Tubing rupture combines raceway rupture with other tubing rupture.

Source: data are from Paden et al. [6].

### Table 32.6 Patient-related complications of extracorporeal life support

<table>
<thead>
<tr>
<th>Complication</th>
<th>Age group</th>
<th>Cohort</th>
<th>Number of cases (%)</th>
<th>Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cannula site bleeding</td>
<td>Neonatal</td>
<td>Respiratory</td>
<td>1845 (7.2%)</td>
<td>64%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cardiac</td>
<td>513 (10.5%)</td>
<td>29%</td>
</tr>
<tr>
<td></td>
<td>Pediatric</td>
<td>Respiratory</td>
<td>870 (16.4%)</td>
<td>51%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cardiac</td>
<td>830 (14.3%)</td>
<td>46%</td>
</tr>
<tr>
<td>Surgical site bleeding</td>
<td>Neonatal</td>
<td>Respiratory</td>
<td>1605 (6.3%)</td>
<td>44%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cardiac</td>
<td>1540 (31.6%)</td>
<td>30%</td>
</tr>
<tr>
<td></td>
<td>Pediatric</td>
<td>Respiratory</td>
<td>756 (14.3%)</td>
<td>46%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cardiac</td>
<td>1836 (31.7%)</td>
<td>42%</td>
</tr>
<tr>
<td>Cardiac tamponade (blood/serous/air)</td>
<td>Neonatal</td>
<td>Respiratory</td>
<td>201 (0.7%)</td>
<td>40%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cardiac</td>
<td>317 (6.5%)</td>
<td>29%</td>
</tr>
<tr>
<td></td>
<td>Pediatric</td>
<td>Respiratory</td>
<td>141 (2.6%)</td>
<td>36%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cardiac</td>
<td>327 (5.6%)</td>
<td>43%</td>
</tr>
<tr>
<td>Seizures (determined clinically)</td>
<td>Neonatal</td>
<td>Respiratory</td>
<td>2411 (9.4%)</td>
<td>61%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cardiac</td>
<td>363 (7.5%)</td>
<td>29%</td>
</tr>
<tr>
<td></td>
<td>Pediatric</td>
<td>Respiratory</td>
<td>311 (5.9%)</td>
<td>34%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cardiac</td>
<td>419 (7.2%)</td>
<td>24%</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>Neonatal</td>
<td>Respiratory</td>
<td>1785 (7%)</td>
<td>44%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cardiac</td>
<td>548 (11.3%)</td>
<td>23%</td>
</tr>
<tr>
<td></td>
<td>Pediatric</td>
<td>Respiratory</td>
<td>316 (6%)</td>
<td>22%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cardiac</td>
<td>277 (4.7%)</td>
<td>26%</td>
</tr>
</tbody>
</table>

Patient-related complications of extracorporeal life support (ECLS) divided into age group and cohort. Pediatric refers to the age range 1 month–16 years. Respiratory cohort refers to those with a respiratory indication for ECLS. Cardiac cohort refers to those with a cardiovascular indication for ECLS.

Source: data are from Paden et al. [6].
ECMO for respiratory support

The introduction of ECMO programs for neonates with respiratory failure produced significant improvement in outcome, 82% survival vs. 72% for historical controls [155]. Of the 51,000 patients requiring ECMO recorded to the ELSO Registry through 2012, 50% were for neonatal respiratory support and recent data reveal a 65–70% survival to discharge in this population [6].

Outside the neonatal period, pediatric outcomes varies depending on both diagnosis (e.g., 83% survival for asthma, 23% for fungal pneumonia) and co-morbidity (e.g., 59% for chronic lung disease, 5% for hematopoietic stem cell transplant) [156]. Survival declines with increasing time on mechanical support. In a study of 3,213 children supported on ECMO, those requiring < 14 days of support had 61% survival compared with 38% in those supported for more than 21 days. Male gender, increased inotrope infusion, and acidosis were independently associated with increased odds of death [157].

ECMO complicated by sepsis

Mechanical support involves long-term invasive cannulas and access ports for sampling in critically ill patients who may be immunosuppressed, placing patients at significant risk of infection. Examination of the ELSO registry from 1998 to 2008 found that infections occurred in 11.7% of patients who were on ECMO. For adult, pediatric, and neonatal groups, the rates were 30.6, 20.8, and 10.1 infections per 1,000 ECMO days, respectively. Venoarterial ECMO was associated with the highest rate of infection in each group. As expected, the prevalence of infection increases with time on mechanical support: 61% infection rate for < 7 days ECMO, 30.3% in those requiring ECMO for > 14 days [158]. The most common organisms were coagulase-negative staphylococci in the neonatal group (15.9% of all patients) and Candida in the older pediatric and adult groups (12.7% of all patients). Pseudomonas aeruginosa was grown in 10.5% and Staphylococcus aureus in 9.4%. Overall, those with culture-positive infections on ECMO had longer ECMO runs and a higher rate of death (57.6% infected vs. 41.5% non-infected). Even though fungal infections before and during extracorporeal support confer increased mortality, the presence of a fungal infection before ECMO is not a contraindication to support [159]. The incidence of these infections may be reduced by similar strategies to those for central line infections and ventilator-associated pneumonia [158].

ECMO and renal function

Renal function in the context of ECMO or CPB may be adversely affected due to hemodynamic impairment, ischemia–reperfusion injury, inflammation, and oxidative stress. Definitions of acute kidney injury (AKI) vary and the ELSO registry data collection uses a high threshold of serum creatinine for their definition (>1.5 mg/dL), so AKI in smaller patients may be missed [160] and single-center reports of AKI differ from the ELSO registry data. With this in mind, data extracted from ELSO for neonates and older children are presented in Table 32.7. Note that the incidence of AKI in the cardiac ECMO groups is higher than those in the respiratory groups. In addition, the presence of renal dysfunction in all groups is associated with a higher mortality.

Overall long-term survival

It would be shortsighted to restrict our focus on hospital discharge, as the combination of mechanical support and underlying disease will have a longer-lasting effect on the child’s health [161]. Data are starting to reveal that the incidence of late death is significant. In a study of 741 children requiring ECMO, 469 survived past 90 days. Of those survivors, 46 (10%) subsequently died. Of the children alive at 90 days, the highest survival was for meconium aspiration syndrome (MAS) (97.9%) and the lowest survival was for congenital diaphragmatic hernia (73.6%). Congenital and acquired heart disease also carried a significantly increased risk of late death compared with MAS; in these cardiac patients, the most common cause of late death was cardiac failure, although some deaths were due to neurological injury, respiratory failure, and renal failure. ECLS for CHD had an estimated 5-year survival after ECMO of 32.3%. Surprisingly, some late deaths were in children with an underlying diagnosis of myocarditis who had apparently been successfully weaned from ECMO after the acute illness [162]. As expected, in those who required ECLS for respiratory disease, the causes of late deaths were mostly due to respiratory failure or pulmonary hypertension. Many of the other deaths were due to complications of prematurity [162]. We can therefore conclude that for cardiac and respiratory indications for ECMO, almost all of the late deaths were related to the primary underlying disease rather than complications of the mechanical support itself.

Neurological outcome

Brain injury is common in children receiving mechanical support. A nationwide study in the Netherlands reviewed ultrasound images over 20 years on all neonates (>2 kg and >34 weeks gestation) who received ECMO. The overall incidence of injury was 17.3%, of which 8.8% had a primary hemorrhage. Stroke occurred in 5% and lobar hematoma in 2.2%. Survival of patients without brain injury was 75.5% compared with 54.7%, and the incidence of brain injury in preterm neonates was 31.5% compared with those born at term (14.5%). As expected, three-quarters of the premature brain injury was primary hemorrhage. It is notable that the prevalence of brain injury did not differ over the 20-year time span, despite alterations in the technical management of the ECMO circuit [163].

Seizures are common in children treated with ECMO, and recent evidence suggests we may be underestimating the true incidence. In one small study of 19 non-neonatal
Table 32.7 Renal injury during extracorporeal life support

<table>
<thead>
<tr>
<th>Age group</th>
<th>Indication for support</th>
<th>Degree of acute kidney injury (AKI)</th>
<th>Number reported with AKI (% of total)</th>
<th>Survival number (% of total)</th>
<th>Cohort survival to discharge or transfer (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal</td>
<td>Respiratory</td>
<td>(\text{Cr}_{\text{serum}} \leq 1.5 \text{ mg/dL})</td>
<td>1,782 (7%)</td>
<td>914 (51%)</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(\text{Cr}_{\text{serum}} &gt; 1.5 \text{ mg/dL})</td>
<td>345 (1.3%)</td>
<td>126 (37%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Renal support required</td>
<td>(\text{Cr}_{\text{serum}} \leq 1.5 \text{ mg/dL})</td>
<td>5,067 (20%)</td>
<td>2552 (50.3%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(\text{Cr}_{\text{serum}} &gt; 1.5 \text{ mg/dL})</td>
<td>617 (12.7%)</td>
<td>138 (22%)</td>
<td>39%</td>
</tr>
<tr>
<td></td>
<td>Renal support required</td>
<td>(\text{Cr}_{\text{serum}} \leq 1.5 \text{ mg/dL})</td>
<td>92 (1.9%)</td>
<td>24 (26%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(\text{Cr}_{\text{serum}} &gt; 1.5 \text{ mg/dL})</td>
<td>2,038 (42%)</td>
<td>476 (23.3%)</td>
<td></td>
</tr>
<tr>
<td>Pediatric</td>
<td>Respiratory</td>
<td>(\text{Cr}_{\text{serum}} \leq 1.5 \text{ mg/dL})</td>
<td>521 (9.9%)</td>
<td>162 (31%)</td>
<td>56%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(\text{Cr}_{\text{serum}} &gt; 1.5 \text{ mg/dL})</td>
<td>242 (4.6%)</td>
<td>69 (29%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Renal support required</td>
<td>(\text{Cr}_{\text{serum}} \leq 1.5 \text{ mg/dL})</td>
<td>2,297 (43.6%)</td>
<td>909 (39.5%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(\text{Cr}_{\text{serum}} &gt; 1.5 \text{ mg/dL})</td>
<td>684 (11.8%)</td>
<td>195 (28.5%)</td>
<td>48%</td>
</tr>
<tr>
<td></td>
<td>Renal support required</td>
<td>(\text{Cr}_{\text{serum}} \leq 1.5 \text{ mg/dL})</td>
<td>261 (4.5%)</td>
<td>79 (30%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(\text{Cr}_{\text{serum}} &gt; 1.5 \text{ mg/dL})</td>
<td>2,215 (38.3%)</td>
<td>761 (34.3%)</td>
<td></td>
</tr>
</tbody>
</table>

The association of AKI with extracorporeal life support (ELSO) stratified according to neonates < 30 days old and pediatrics (1 month–16 years). Renal replacement therapy refers to those requiring dialysis, hemofiltration or continuous arteriovenous hemodialysis.

Source: data are from Paden et al. [6].

Pediatric patients, four children had seizure activity, of which three were non-convulsive. Although the seizures were not associated with mortality, the abnormal EEG activity often occurred in the absence of associated clinical findings. This seizure activity may indicate CNS injury [164], although the neurological outcome in this population was unknown. It is known, however, that neonates treated with ECMO who had seizures have a higher risk of developmental delay [165].

Sensorineural hearing loss has also been reported in patients after ECMO. Risk factors include prolonged ECMO, ICH, sepsis, and seizures [166]. In 136 neonatal ECMO survivors followed up to 5–12 years of age, the incidence of bilateral sensorineural hearing loss > 20 dB was 3.7%; however, median intelligence and language development were normal.

### Quality of life

It is known that neurological injury is common during ECMO, as is long-term cardiac and respiratory dysfunction, and now data are emerging regarding quality of life. This is problematic to assess due to the difficulty of defining “quality of life” and delineating the effects of ECMO from those of the underlying disease. With these caveats in mind, one study concluded that neonates who had been on ECMO were found to have a significantly worse health-related quality of life at 5 years of age compared with a healthy reference group based on mater- nal reported health-related quality of life scores. The indications for ECMO were mostly respiratory disease. In particular, delayed neuromotor development, cognitive, and behavior problems and a disabled maximum exercise capacity affected the outcome [167]. Another study looking at pediatric cardiac ECMO survivors also found their maternal reported health-related quality of life to be lower than that of the controls, but similar to children with complex cardiac disease, whereas the psychosocial quality of life was similar to the general population. Interestingly, the children old enough to report on their own questionnaire suggest the their quality of life is equal to or better than that of their peers [168]. Overall, regardless of the range of psychosocial and physical disabilities, long-term survivors of CHD requiring ECMO report their quality of life to be quite good [169].

### Comparing outcomes and complications of VAD and ECMO

It is not always possible to directly compare outcomes after ECMO with those of VAD in view of their differing roles, timing of use, indications, and practicalities. ECMO is more familiar and more commonly used in children because VAD cannot provide respiratory support, nor can it be used for pulmonary hypertension. As a result, VAD has a lower prime volume, causes less hemolysis, has a reduced requirement for anticoagulation and reduced bleeding complications. The VAD circuit has fewer ports of access, which reduces the chance of infection, and the patient can also be mobilized. In addition, the time-dependent increase in complications seen with ECMO does not seem to be as evident with VAD [99]. Long-term support with VAD is therefore associated with fewer ECLS-related complications while bridging to recovery or transplant.

Recent advances in VAD devices have been made the Berlin Heart EXCOR® (described earlier) the treatment standard for pediatric bridge to transplantation in the USA [10]. For children without single-ventricle physiology or end-organ dysfunction, a trial on the use of
the Berlin Heart EXCOR® showed a rate of successful bridge to transplant or recovery of approximately 90%, with a 29% rate of neurological injury [10]. In a larger, less selective multicenter trial, children supported for 1–435 days showed a 12-month survival of 75%, which comprised 64% successfully transplanted, 6% recovered and explanted, and 5% with device in situ at 12 months. The most common cause of death while on EXCOR was respiratory failure (50% of deaths), while 33% of deaths were due to neurological injury, with thromboembolic strokes being more common than hemorrhagic strokes. Lower patient size (and age) was also associated with early mortality. Mortality appeared to reduce in centers with higher numbers of implantations; however, this difference was not significant when adjusted for other baseline characteristics [10].

Although there are no large studies comparing ECMO and VAD used as a bridge to transplantation, this study reveals improved survival for children > 5 kg supported by EXCOR compared with outcomes of long-term ECMO. The survival for children < 5 kg in the study was poor; 21 out of 33 died, so the advantage over ECMO seen in larger children has yet to be demonstrated in this group [10]. A small comparative study in children has shown significantly improved survival with Berlin Heart EXCOR over ECMO as a bridge to transplant, with a comparable risk of neurological injury [35].

From the physiological point of view, a study in piglet models comparing ECMO with pulsatile and continuous-flow VADs showed improved left ventricular blood supply/demand ratio in both VAD and ECMO groups. In addition, left ventricular filling pressures and left ventricular workload were similarly reduced in the pulsatile VAD and ECMO groups; however, VAD demonstrated improved global myocardial blood supply/demand ratio compared with ECMO [170]. It is not yet known whether these cardiovascular changes induced by VAD would lead to improved reversed ventricular remodeling of the myocardium.

**Other outcome issues**

**Volume of cases**

A recent retrospective study of 7,322 pediatric patients supported with ECMO found that after adjusting for case mix, surgery complexity, and year of treatment, the low-volume centers (average < 20 cases per year) had significantly higher odds of death compared with the medium- and higher-volume centers; the minimum annual caseload associated with lower mortality was 22 [171].

**Parental outcomes**

A study of the parents of children who were successfully bridged to recovery demonstrated that 20% suffered symptoms of post-traumatic stress disorder. This has potential implications for the information we deliver to parents. Screening and developing service interventions for parents who are suffering from these symptoms are advised [172].

**KEY POINTS: COMPLICATIONS AND OUTCOMES OF MCS**

- Survival after ECMO is significantly better when used for respiratory support than when used for cardiac support.
- Survival among patients requiring cardiac support is significantly better for cardiomyopathy than for post-cardiotomy patients.

**The future**

Mechanical devices to support of the circulation are rapidly changing, their use is increasing, and patient survival has improved. The following factors should be considered when evaluating new mechanical support devices as they are developed: safety and reliability, operator interface, portability, cost, differential modes, and data retention. Soon on the horizon, low prime devices may allow an asanguineous prime for neonatal ECMO, further reducing the time to provide support. In the USA, the National Heart, Lung, and Blood Institute supports research into new pediatric cardiac assist systems, and one system under development by Enson Inc. (Pittsburgh, PA), integrates a pump and oxygenator and is capable of providing both cardiac and pulmonary support to neonates and small children. This device, the pediatric cardiopulmonary assist system (pCAS), is intended for short-term stabilization of preoperative neonatal and infant patients or patients requiring postoperative support. The integrated pCAS design is a novel idea that results in a single component heart–lung system with the advantages of reduced priming volume and blood-contacting surface area. Many other devices are under development and it is difficult to predict which devices will develop to improve patient outcomes, but it is certainly clear that this is a rapidly changing field of applied technology.

**Selected references**

A full reference list for this chapter is available at: http://www.wiley.com/go/andropoulos/congenitalheart

6 Paden ML, Conrad SA, Rycus PT, Thiagarajan RR.. Extracorporeal Life Support Organization Registry Report 2012. ASAIO J 2013;59:202–10. Nearly 51,000 patients have received ECLS. Use of ECLS for cardiac support represents a large area of consistent growth. Approximately 13,000 patients have been treated, with survival to discharge rates of 40%, 49%, and 39% for neonates, pediatric, and adults, respectively.

18 del Nido PJ, Dalton HJ, Thomson AE et al. Extracorporeal Membrane Oxygenator rescue in children during cardiac arrest after cardiac surgery. Circulation 1992;86:II 300–4. This is the first article to demonstrate the benefit of ECMO as rescue for cardiac arrest, termed ECPR. Overall early survival was seven of
11 (64%), with one patient requiring heart transplantation due to irreversible cardiac dysfunction. One child died late (1 month) after ECMO support. There were no long-term sequelae in the survivors.

22 McMullan DM, Thiagarajan RR, Smith KM, et al. Extracorporeal cardiopulmonary resuscitation outcomes in term and premature neonates. Pediatr Crit Care Med 2014;15:e9–16. These authors retrospectively reviewed data from the ELSO registry from 1998 to 2010 where ECMO was used for resuscitation. Overall survival to hospital discharge for the 641 neonates who received ECPR was 39. In the multivariate analysis, lower birth weight and pre-extracorporeal cardiopulmonary resuscitation oxygenation, as well as complications including CNS hemorrhage, pulmonary hemorrhage, acidosis, renal replacement therapy, and mechanical complications, increased the odds of death.

34 Chen JM, Richmond ME, Charette K et al. A decade of pediatric mechanical circulatory support before and after cardiac transplantation. J Thorac Cardiovasc Surg 2012;143:344–51. Thirty-seven patients received VADs; 32 (86.5%) survived to transplantation. No difference in post-transplant survival was demonstrated between those patients supported with either ECMO or VAD before transplant and all others not bridged to transplantation.

44 Hoganson DM, Gazit AZ, Boston US, et al. Paracorporeal lung assist devices as a bridge to recovery or lung transplantation in neonates and young children. J Thorac Cardiovasc Surg 2014;147:420–7. One neonate (23 days old) and three young children (aged 2, 9, and 23 months) presented with primary lung disease with pulmonary hypertension. One patient was bridged to lung transplant (9 months old, with alveolar capillary dysplasia, supported 5 days). One patient was bridged to recovery with maximal medical therapy (23 months old, with primary pulmonary hypertension, supported 23 days). Two patients died while awaiting a suitable lung donor after a support time of 54 and 72 days.

55 MacLaren G, Butt W, Best D. Central extracorporeal membrane oxygenation for refractory pediatric septic shock. Pediatr Crit Care Med 2011;12:133–6. Twenty-three patients (median age, 6 years; median weight, 20 kg) were included. Eighteen (78%) patients survived to be decannulated off ECMO, and 17 (74%) children survived to hospital discharge. Higher pre-ECMO arterial lactate levels were associated with increased mortality (11.7 mmol/L in non-survivors vs. 6.0 mmol/L in survivors, P = 0.007).

69 Fraser Jr., CD, Jaquiss RB, Rosenthal DN, et al. Prospective trial of a pediatric ventricular assist device. N Engl J Med 2012;367:532–41. Reports results of the US trial of the Berlin Heart VAD, a prospective, single-group trial as a bridge to heart transplantation. Patients 16 years of age or younger were divided into two cohorts according to BSA (cohort 1, < 0.7 m²; cohort 2, 0.7 to < 1.5 m²), with 24 patients in each group. Survival in the two cohorts receiving mechanical support was compared with survival in historical control groups undergoing ECMO. For participants in cohort 1, the median survival time had not been reached at 174 days, whereas in the matched ECMO group, the median survival was 13 days (P < 0.001). For participants in cohort 2 and the matched ECMO group, the median survival was 144 days and 10 days, respectively (P < 0.001).

130 Mascio CE, Austin III, EH, Jacobs JP. Perioperative mechanical circulatory support in children: An analysis of the Society of Thoracic Surgeons Congenital Heart Surgery Database. J Thorac Cardiovasc Surg 2014;147:658–65. Of 96,596 operations (80 centers), MCS was used in 2.4%. The MCS patients were younger (13 vs. 195 days, P < 0.0001) and more often had STS-defined preoperative risk factors (57.2% vs. 32.7%, P < .0001).

162 Iguchi A, Ridout DA, Galan S, et al. Long term survival outcomes and causes of late death in neonates, infants and children treated with extracorporeal life support. Pediatr Crit Care Med 2013;14:580–6. A total of 741 children with 272 early deaths (36.7%) and 46 late deaths (6.2%) were included. Median follow-up time in survivors was 7.1 (interquartile range, 3.0–11.9) years. There was increased risk of late death in congenital diaphragmatic hernia, CHD, and acquired heart disease (P < 0.001, P < 0.01, P = 0.01) in comparison with the risk in meconium aspiration syndrome.

163 Raets MMA, Dudink J, Ijsselstijn H, et al. Brain injury associated with neonatal extracorporeal membrane oxygenation in the Netherlands: a nationwide evaluation spanning two decades. Pediatr Crit Care Med 2013;14:884–92. Brain abnormalities were detected in 17.3%; primary hemorrhage was most frequent (8.8%). Stroke was identified in 5% of the total group, with a notable significant preference for the left hemisphere (in 70%). Lobar hematoma (prevalence 2.2 %) was also significantly left predominant.
Appendix: Texas Children’s Hospital
Pediatric Cardiovascular Anesthesia
Drug Sheet (April 2015)

Lisa A. Caplan and Erin A. Gottlieb

Drug doses and treatments are those commonly recommended; each patient’s treatment must be individualized, drug doses double-checked for accuracy, and drug concentrations and modes of administration used according to local guidelines. The information here is current at the time of publication; however, the practitioner must always be aware of new recommendations, and remains responsible for determining the best course of treatment. Consult the textbook, hospital formulary, or authoritative internet resources for a complete listing of indications, contraindications, interval dosing schedules, and side-effects of these drugs and treatments. All drugs are intravenous, unless otherwise noted. Drugs denoted with an asterisk (*) are not approved by the US Food and Drug Administration (FDA) as of April 2015. Many drugs are not specifically labeled for pediatric use by the US FDA; however, the physician may choose to administer these drugs for specific indications, if in their judgment the drug will be safe and effective. The source for dosing information is the Texas Children’s Hospital formulary, current as of April 2015, except as otherwise noted in the references.
### Vasoactive infusions

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Range</th>
<th>Loading Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clevidipine [1]</td>
<td>0.5–7 μg/kg/min</td>
<td>10–15 μg/kg</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>2–20 μg/kg/min</td>
<td></td>
</tr>
<tr>
<td>Dopamine</td>
<td>2–20 μg/kg/min</td>
<td></td>
</tr>
<tr>
<td>Epinephrine</td>
<td>0.03–1 μg/kg/min</td>
<td></td>
</tr>
<tr>
<td>Esmolol</td>
<td>200–1,000 μg/kg/min</td>
<td>Loading: 100–500 μg/kg</td>
</tr>
<tr>
<td>Epoprostenol</td>
<td>1–2 ng/kg/min initial infusion; increase by 1–2 ng/kg/min every 4–8 hours to 25–40 ng/kg/min; must be given in dedicated intravenous line</td>
<td></td>
</tr>
<tr>
<td>Fenoldopam</td>
<td>0.1–0.8 μg/kg/min</td>
<td></td>
</tr>
<tr>
<td>Isoprotrenol</td>
<td>0.03–1 μg/kg/min</td>
<td>Maximum dose 2 μg/kg/min</td>
</tr>
<tr>
<td>Levosimendan [2]</td>
<td>0.05–1 μg/kg/min</td>
<td>Loading: 6–12 μg/kg over 1 hour</td>
</tr>
<tr>
<td>Liothyronine (Triostat®, T₃) [3,4]</td>
<td>0.05–0.15 μg/kg/hour</td>
<td></td>
</tr>
<tr>
<td>Milrinone</td>
<td>0.25–0.75 μg/kg/min</td>
<td>Loading: 50 μg/kg over 10–60 minutes</td>
</tr>
<tr>
<td>Nesiritide</td>
<td>0.01 μg/kg/min; at intervals of 3 hours, dosage may be increased by 0.005 μg/kg/min to a maximum of 0.03 μg/kg/min</td>
<td></td>
</tr>
<tr>
<td>Nicardipine</td>
<td>0.5–2 μg/kg/min</td>
<td></td>
</tr>
<tr>
<td>Nitroglycerine</td>
<td>0.25–3 μg/kg/min</td>
<td></td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>0.3–3 μg/kg/min</td>
<td></td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>0.03–1 μg/kg/min</td>
<td></td>
</tr>
<tr>
<td>Phenytoine</td>
<td>0.05–0.5 μg/kg/min</td>
<td></td>
</tr>
<tr>
<td>Prostaglandin E1</td>
<td>0.01–0.1 μg/kg/min</td>
<td></td>
</tr>
<tr>
<td>Sildenafil [5,6]</td>
<td>0.067 mg/kg/hour</td>
<td>Loading: 0.4 mg/kg over 3 hours</td>
</tr>
<tr>
<td>Treprostinil</td>
<td>0.625–1.25 ng/kg/minute; must be given in dedicated intravenous line</td>
<td></td>
</tr>
<tr>
<td>Vasopressin</td>
<td>0.01–0.04 units/kg/hour</td>
<td></td>
</tr>
</tbody>
</table>

### Vasoactive bolus drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atropine</td>
<td>IV</td>
<td>0.01–0.02 mg/kg</td>
</tr>
<tr>
<td></td>
<td>IM</td>
<td>0.02 mg/kg</td>
</tr>
<tr>
<td>Calcium chloride</td>
<td>IV</td>
<td>10 mg/kg</td>
</tr>
<tr>
<td>Calcium gluconate</td>
<td>IV</td>
<td>30 mg/kg</td>
</tr>
<tr>
<td>Enalaprilat</td>
<td>IV</td>
<td>5–10 μg/kg/dose IV Q8–24H; max. 5 mg/dose</td>
</tr>
<tr>
<td>Ephedrine</td>
<td>IV</td>
<td>0.1 mg/kg max. 5 mg</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>IV</td>
<td>0.5–10 μg/kg IV</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>IV</td>
<td>0.1–0.2 mg/kg IV</td>
</tr>
<tr>
<td>Labetalol</td>
<td>IV</td>
<td>0.2–1 mg/kg</td>
</tr>
<tr>
<td>Methylene blue [7–9]</td>
<td>IV</td>
<td>1–2 mg/kg</td>
</tr>
<tr>
<td>Phenoxybenzamine</td>
<td>IV</td>
<td>0.25–1 mg/kg</td>
</tr>
<tr>
<td>Phentolamine</td>
<td>IV</td>
<td>0.05–0.2 mg/kg</td>
</tr>
<tr>
<td>Phenytoine</td>
<td>IV</td>
<td>0.5–3 μg/kg</td>
</tr>
</tbody>
</table>

### Antiarrhythmic agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenosine</td>
<td>First dose: 0.1 mg/kg IV (max. 6 mg) Second dose: 0.2 mg/kg IV (max. dose 12 mg)</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>10–15 mg/kg/day</td>
</tr>
<tr>
<td></td>
<td>Loading: 2.5–5 mg/kg or a maximum of 300 mg IV over 5–10 min. Additional boluses of 5 mg/kg or a maximum of 150 mg IV push may be given with a maximum total dose not to exceed 25 mg/kg or 2.2 g in 24 hours</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>20–50 μg/kg/min</td>
</tr>
<tr>
<td></td>
<td>Loading: 1 mg/kg; repeat if the dose infusion is initiated more than 15 minutes after initial bolus</td>
</tr>
<tr>
<td>Procainamide</td>
<td>20–80 μg/kg/min (max. 2 g/day)</td>
</tr>
<tr>
<td></td>
<td>Loading: 3–6 mg/kg/dose over 5 minutes, not to exceed 100 mg/dose; may repeat every 5–10 minutes to maximum total loading dose of 15 mg/kg; do not exceed 500 mg in 30 minutes</td>
</tr>
<tr>
<td>Verapamil</td>
<td>0.1–0.3 mg/kg/dose (max. 5 mg) Repeat dose 30 minutes after initial dose as needed (max. second dose 10 mg)</td>
</tr>
</tbody>
</table>
### Anesthetic/analgesia agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage/Concentration</th>
<th>Notes/Loading/Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>10–15 mg/kg IV Q6H</td>
<td></td>
</tr>
<tr>
<td>Dexmedetomidine</td>
<td>0.25–0.75 μg/kg/hour</td>
<td>Loading: 0.25–1.0 μg/kg over 10 minutes</td>
</tr>
<tr>
<td>Etomidate</td>
<td>0.2–0.3 mg/kg</td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td>0.25–1.0 μg/kg/hour</td>
<td>Infusion: 1–10 μg/kg/hour</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>0.005–0.015 mg/kg</td>
<td>Maximum single dose: 2 mg</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>10 mg/kg IV Q6–8H</td>
<td></td>
</tr>
<tr>
<td>Ketamine</td>
<td>IV: 1–2 mg/kg IM: 5–10 mg/kg</td>
<td>6 hours (max. 30 mg/dose; 120 mg/day)</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>0.5–1 mg/kg IV; 0.5 mg/kg/dose every 6 hours (max. 30 mg/dose; 120 mg/day)</td>
<td></td>
</tr>
<tr>
<td>Midazolam</td>
<td>0.03–0.1 mg/kg IV</td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>0.05–0.2 mg/kg IV</td>
<td></td>
</tr>
<tr>
<td>Remifentanil</td>
<td>0.025–2 μg/kg/min</td>
<td>Loading: 0.5–1 μg/kg IV</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>0.1–0.3 μg/kg/hour</td>
<td>Loading: 1–2 μg/kg IV</td>
</tr>
</tbody>
</table>

### Muscle relaxants (intubation dose) and reversal of neuromuscular blockade

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atracurium</td>
<td>0.4–0.5 mg/kg IV</td>
<td></td>
</tr>
<tr>
<td>Cisatracurium</td>
<td>0.1 mg/kg IV</td>
<td></td>
</tr>
<tr>
<td>Pancuronium</td>
<td>0.1 mg/kg IV</td>
<td></td>
</tr>
<tr>
<td>Rocuronium</td>
<td>0.6–1.2 mg/kg IV</td>
<td></td>
</tr>
<tr>
<td>Succinylcholine</td>
<td>1–2 mg/kg IV; 4 mg/kg IM</td>
<td></td>
</tr>
<tr>
<td>Vecuronium</td>
<td>0.08–0.1 mg/kg IV</td>
<td></td>
</tr>
<tr>
<td>Neostigmine</td>
<td>50–70 μg/kg IV</td>
<td></td>
</tr>
<tr>
<td>Glycopyrrolate</td>
<td>10–14 μg/kg IV (with neostigmine)</td>
<td></td>
</tr>
<tr>
<td>Sugammadex [10]*</td>
<td>2–4 mg/kg IV</td>
<td></td>
</tr>
</tbody>
</table>

### Antibiotics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>50 mg/kg IV (max 2 g)</td>
<td></td>
</tr>
<tr>
<td>Cefazolin</td>
<td>25–30 mg/kg IV (max 1 g)</td>
<td></td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>25–50 mg/kg IV (max 1.5 g)</td>
<td></td>
</tr>
<tr>
<td>Clindamycin</td>
<td>10–13 mg/kg IV (max 900 mg)</td>
<td></td>
</tr>
<tr>
<td>Gentamicin</td>
<td>1–2.5 mg/kg IV (max 120 mg)</td>
<td></td>
</tr>
<tr>
<td>Nafcillin</td>
<td>37.5–50 mg/kg IV (max 2 g)</td>
<td></td>
</tr>
<tr>
<td>Piperacillin/tazobactam</td>
<td>50–100 mg/kg IV piperacillin component (max 16 g piperacillin component/day)</td>
<td></td>
</tr>
<tr>
<td>Vancomycin</td>
<td>10–15 mg/kg IV (max 1 g)</td>
<td></td>
</tr>
</tbody>
</table>

### Antiemetics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metaclopramide</td>
<td>0.1–0.2 mg/kg/dose IV every 6–8 hours as needed (max. 10 mg)</td>
<td></td>
</tr>
<tr>
<td>Ondansetron</td>
<td>0.1 mg/kg IV (max. 4 mg)</td>
<td></td>
</tr>
</tbody>
</table>

### Corticosteroids

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone</td>
<td>Antiemetic: 0.15–0.5 mg/kg IV</td>
<td>Airway edema: 0.25–0.5 mg/kg IV</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>Adrenal insufficiency (stress dose): 50–100 mg/m²/dose IV</td>
<td>Anaphylaxis 0.5–2 mg/kg (max. 250 mg)</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>20–30 mg/kg IV bolus or to bypass circuit</td>
<td></td>
</tr>
</tbody>
</table>

### Diuretics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bumetanide</td>
<td>0.1 mg/kg/dose (IV or PO)</td>
<td></td>
</tr>
<tr>
<td>Furosemide</td>
<td>0.5–1 mg/kg IV (max 20 mg)</td>
<td></td>
</tr>
<tr>
<td>Mannitol</td>
<td>0.25–2 g/kg IV</td>
<td></td>
</tr>
</tbody>
</table>
### Antifibrinolytics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Neonate 0–2 mo.</th>
<th>Infant 2–12 mo.</th>
<th>Child &gt;12 mo.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tranexamic acid [11,12]</td>
<td>15 mg/kg bolus; 20 mcg/ml of CPB prime; 2.5 mg/kg/hr infusion. Infant 2–12 mo.: 9 mg/kg bolus; 20 mcg/ml of CPB prime; 2 mg/kg/hr infusion. Child &gt;12 mo.: 4 mg/kg bolus; 20 mcg/ml of CPB prime; 2 mg/kg/hr infusion.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aprotinin&lt;sup&gt;a&lt;/sup&gt;</td>
<td>28,000–60,000 KIU bolus; 28,000–60,000 KIU/kg to CPB prime, 3,500–7,000 KIU/kg/hr infusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epsilon aminocaproic acid [13]</td>
<td>Neonate 0–2 mo.: 40 mg/kg bolus; 0.1 mg/ml of CPB prime; 30 mg/kg/hr infusion. Infant 2–12 mo. and child &gt;12 mo.: 75 mg/kg bolus; 75 mg/kg for CPB prime; 75 mg/kg/hr infusion.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Anticoagulants and reversal

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bivalirudin [14]</td>
<td>1 mg/kg IV bolus; additional bolus of 0.1–0.5 mg/kg for subtherapeutic ACT; 50 mg to bypass circuit; infusion 2.5 mg/kg/hr</td>
</tr>
<tr>
<td>Heparin</td>
<td>300–400 units/kg (3–4 mg/kg) for CPB; 100 units/kg (1 mg/kg) for heparinization for non-CPB cases (e.g., coarctation of aorta, systemic-to-pulmonary artery shunt)</td>
</tr>
<tr>
<td>Protamine</td>
<td>1–1.3 times heparin dose in mg</td>
</tr>
</tbody>
</table>

### Electrolytes

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium bicarbonate</td>
<td>1 mEq/kg; dilute 1:1 with sterile water for neonates</td>
</tr>
<tr>
<td>THAM (tromethamine)</td>
<td>1 mL/kg IV of 0.3 M solution; subsequent dosing based on blood gas result</td>
</tr>
<tr>
<td>Potassium chloride</td>
<td>0.5–1 mEq/kg IV over 1 hour</td>
</tr>
<tr>
<td>Magnesium sulfate</td>
<td>25–50 mg/kg IV over 1 hour</td>
</tr>
<tr>
<td>Dextrose</td>
<td>For the treatment of hypoglycemia D&lt;sub&gt;10&lt;/sub&gt;: 3–5 mL/kg IV for neonates D&lt;sub&gt;25&lt;/sub&gt;: 1–2 mL/kg IV for age 3 months to 2 years D&lt;sub&gt;50&lt;/sub&gt;: 0.5–1 mL/kg IV for age &gt; 2 years</td>
</tr>
</tbody>
</table>

### Miscellaneous drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphenhydramine</td>
<td>For acute hypersensitivity 1–2 mg/kg IV (max. 50 mg/dose)</td>
</tr>
<tr>
<td>Flumazenil</td>
<td>1–5 μg/kg IV; repeat as necessary</td>
</tr>
<tr>
<td>Levoalbuterol</td>
<td>4–8 puffs MDI through ETT; may repeat</td>
</tr>
<tr>
<td>Naloxone</td>
<td>1–10 μg/kg IV; repeat as necessary</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>1 mg/kg IV</td>
</tr>
</tbody>
</table>

### Oral/intranasal premedications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexmedetomidine</td>
<td>Intranasal: 2 μg/kg</td>
</tr>
<tr>
<td>Ketamine</td>
<td>Oral: 5–10 mg/kg</td>
</tr>
<tr>
<td>Midazolam</td>
<td>Intranasal: 0.2 mg/kg over 15 seconds, may repeat in 5–15 min (max 15 mg) Oral: 0.5–1 mg/kg</td>
</tr>
<tr>
<td>Pentobarbital</td>
<td>Oral: 3–5 mg/kg</td>
</tr>
</tbody>
</table>

### Blood products and volume expanders

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin 5%</td>
<td>10–20 mL/kg IV</td>
</tr>
<tr>
<td>Anti-inhibitor Coagulant Complex</td>
<td>50–100 units/kg; maximum rate of infusion 2 u/kg/min</td>
</tr>
<tr>
<td>Cryoprecipitate</td>
<td>15 mL/5–10 kg IV</td>
</tr>
<tr>
<td>Fibrinogen Concentrate [15]</td>
<td>60–70 mg/kg when fibrinogen level is not known; when fibrinogen level is known Dose (mg/kg) = (100 (mg/dL)—measured level (mg/dL)) divided by 1.7</td>
</tr>
<tr>
<td>Fresh frozen plasma</td>
<td>10–20 mL/kg IV</td>
</tr>
<tr>
<td>Packed red blood cells</td>
<td>10–15 mL/kg IV</td>
</tr>
<tr>
<td>Platelets</td>
<td>1 random unit/5 kg will increase platelet count by 50,000; 1 pheresis unit = 6 random units</td>
</tr>
</tbody>
</table>

<sup>a</sup>Aprotinin was not available in the USA as of December 2007.
Appendix: Texas Children’s Hospital Pediatric Cardiovascular Anesthesia Drug Sheet (April 2015)

<table>
<thead>
<tr>
<th>Prothrombin Complex Concentrate</th>
<th>Pretreatment INR 2–&lt;4: Administer 25 units/kg (max dose 2500 units); Pretreatment INR 4–6: Administer 35 units/kg (max dose 3500 units); Pretreatment INR &gt;6: Administer 50 units/kg (max dose 5000 units)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recombinant factor VIIa [16]</td>
<td>90 μg/kg IV; may repeat dose q 1–2 hours (max. three total doses)</td>
</tr>
<tr>
<td>Whole blood</td>
<td>10–15 mL/kg IV</td>
</tr>
</tbody>
</table>

DC defibrillation/synchronized cardioversion

| Internal defibrillation          | 2 J, increase to 5 J, 10 J                                                                                                                             |
| External defibrillation          | 2–5 J/kg; increase if ineffective to max. 200 J                                                                                                        |
| External synchronized cardioversion| 0.5 J/kg; increase if ineffective to 1 J/kg                                                                                                           |

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