GUEST EDITORIAL

Congenital heart disease

Pediatric Anesthesia is the only anesthesia journal dedicated exclusively to perioperative issues in children undergoing procedures under anesthesia and sedation. It is a privilege to be the guest editor of this special issue dedicated to the care of children with heart disease. The target audience is anesthetists who care for children with heart disease both during cardiac and non-cardiac procedures. The latter takes on increasing importance as children with heart disease undergoing non-cardiac procedures appear to be at a higher risk for cardiac arrest under anesthesia than those without heart disease (1). We hope the articles in this special issue will provide guidelines for management and spark discussions leading to the production of new guidelines.

Over a decade ago Austin et al. (2) demonstrated the benefits of neurological monitoring during heart surgery in reducing adverse neurological outcomes in children. It is not yet standard of care and the current level of evidence supporting its routine use is level 2 (non-randomized controlled trials). However Kasman and Brady (3) wonder if the burden of proof we impose on the cerebral oximeter to improve neurological outcomes is reasonable. The article on transesophageal echocardiography (TEE) by Kamra et al. (4), coupled with the video clips available online, provides a comprehensive overview of TEE in children. Monitoring and treating coagulation disorders after heart surgery (5) and the risks of transfusion are reviewed and provide guidelines for management provided (6).

With improved survival after heart surgery, the number of children with cardiac rhythm management devices (CRMD) has substantially increased. Navaratnam and Dubin (7) present a practical approach on how to care for patients with these devices in the perioperative period. The information on CRMD, along with White’s (8) practical approach to children with heart disease for non-cardiac surgery, provides a framework for managing these patients.

Of the many controversies in the perioperative management of children during heart surgery, glucose control or lack thereof, is high on the list. A recent placebo controlled, large, prospective study of patients in a pediatric intensive care unit reported that ‘tight glycemic control’ resulted in shorter intensive care unit length of stay, reduced lactate levels, decreased C-reactive protein and reduced incidence of infections. However the incidence of hypoglycemia (blood glucose < 40 mg\(^{-1}\) dl) was higher in the intensive insulin treatment group (25%) and the majority (80%) of patients who developed hypoglycemia were infants. (9). Steven and Nicolson take the opposite approach of ‘first do no harm’ (10). If we do not want ‘tight glycemic control’ because of concern about hypoglycemic brain injury, when should we start treating blood sugars? There are no clear answers based on neurological outcomes in children.

Williams and Cohen (11) discuss the care of low birth weight (LBW) infants and their outcomes. Prematurity and LBW are independent risk factors for adverse outcomes after cardiac surgery. Do the anesthetics we use add to this insult? If prolonged exposure to volatile anesthetics is bad for the developing neonatal brain, would avoiding them make for improved outcomes? Wise-Faberowski and Loepke (12) review the current research in search of a clear answer and conclude that there isn’t one. So we muddle along with a mix of anesthetics not sure whether we are helping improve outcomes or not.

For the purist, Wong and Morton (13) present ideas on total intravenous anesthetics and target controlled infusions (TCI). Since ‘early extubation’ and early discharge from the intensive care unit and length of stay are closely tracked by insurance payors, TCI has considerable appeal. Once the patient is in intensive care, managing their pain and sedation becomes important (14).

Children with heart failure are a growing segment of patients for whom pediatric anesthesiologists must care. These children are often subjected to multiple diagnostic tests and interventions for which anesthesia is required. Rosenthal and Hammer (15) discuss the current etiologies and pathogenesis of heart failure and offer ideas for safe perioperative care. Once vasodilator and other medical therapy fails, these children are then placed on mechanical assist devices (16). Finally, some of these children undergo heart transplantation and their perioperative management and outcomes are addressed (17).

Traditionally, mortality has been the outcome measure of success or failure of a surgical program. Thiragarajan and Laussen (18) offer a thoughtful expose on why low mortality should no longer be the yardstick with which to measure success. Other quality indicators are urgently needed if we are to improve the perioperative care of children with heart disease after cardiac surgery.

Doherty and Holbty (19) address the issue of the unavailability of pediatric subspecialists for the care of children with heart disease in developing countries. Finally, as adults with congenital heart disease
(ACHD) now outnumber the children with heart disease, where should the adults be cared for (20)? Will care givers be from the adult world or will they be pediatric subspecialists? Seal (21) reviews current data and discusses their care model in Alberta, Canada, where pediatric cardiac anesthesiologists also manage ACHD. Are we pediatric anesthesiologists or cardiac anesthesiologists specializing in congenital heart disease? Time to ponder.

References


REVIEW ARTICLE

Adult congenital heart disease

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Introduction

In October 2000, the American College of Cardiology hosted the 32nd Bethesda Conference on ‘Care of the Adult with Congenital Heart Disease’. Recommendations were generated pertaining to the organization of health care delivery for adult congenital heart disease (ACHD) including the required health human resources and the educational needs of healthcare providers, access to and continuity of care, as well as meeting the special needs of this population (1–5). Specialized ACHD regional centers with multidisciplinary expertise serving catchment populations of 5–10 million each were proposed. Further, it was advised that these centers should provide a smooth transition from the care previously provided to these patients by pediatric hospitals. Almost a decade later, concerns have been raised about the incomplete realization of these recommendations (6–8).

Prevalence and changing profile

Congenital heart disease (CHD) in children has a prevalence of between 5 and 10 per 1000 live births of which approximately 1.5 per 1000 have complex CHD (1,9–11). In adults, the prevalence of CHD is approximately 4 per 1000 living adults of which 0.38 per 1000 living adults (9%) have complex CHD (9). When ACHD is stratified as simple, moderate, or complex, there are roughly the same numbers of adults in the simple group as in the other two groups combined, and all three groups combined are a smaller population of patients than those having a bicuspid aortic valve (12). The untreated survival of approximately 40% in both the simple and moderate groups improves to 75–80% with treatment. The adult prevalence of severe CHD is increasing as improvements in surgical and medical management result in more than 90% of the children with complex CHD surviving into adulthood compared with the only 15–25% survival for untreated patients, which was seen five decades ago (9,13). In the ACHD population, nearly 50% of patients require ongoing follow-up and further procedures. This matches a predicted need for follow-up in ACHD of >2 per 1000 live births. Following a previous corrective or palliative surgical or interventional cardiac catheterization procedures, half of patients will have two or more surgeries and one-quarter will have three or more surgeries in their lifetime.

Transition from pediatric to adult medical care

Although up to 10% of first presentations may occur in adulthood, most patients with ACHD begin their
cardiac medical care as infants or children. Affiliation of pediatric cardiology programs with an adult ACHD program facilitates the patient’s transition from the pediatric to the adult program and ensures continuity of patient care (14,15). This can be especially challenging in the subset of patients with ACHD who have multiple physical and/or mental disabilities. It is not uncommon for adults with CHD to be living with their parents or to have complex psychosocial needs. Continuity of care may also be compromised by noncompliance in the presence of minimal or no symptoms or with the denial phase, which is common during adolescence. Finally, patients may be lost to follow-up when they move for education or work-related reasons. Other factors such as health care infrastructure and economics in any given country can influence the ACHD patient’s access to care. In the United States, of an approximate burden of a half million adults with complex CHD, it has been estimated that only 30 000 receive follow-up care in a ACHD center (6).

Anesthetic considerations

More detailed information pertaining to the anesthetic considerations in ACHD is available in several review articles (16–18). Detailed information pertaining to the overall assessment and ongoing management of the patient with ACHD may be found on the Internet site of the Canadian Adult Congenital Heart Network, http://www.cachnet.org/index.cgi, as well as in American, British, Canadian, and European Guidelines (15,19–23). The paragraphs that follow explore a number of important general considerations for giving an anesthetic to an adult with CHD for cardiac or non-cardiac surgery.

Preoperative evaluation

Obtaining an accurate history can be problematic as only one-half to three-quarters of adults with CHD can correctly name or describe their diagnosis (24). By limiting their exercise, patients with ACHD may be relatively asymptomatic or have grown accustomed to their condition. Assessment should look for the evidence of long-term cardiac complications and risk factors such as pulmonary hypertension (PHT; threefold risk increment), cyanosis (higher mortality and postoperative complications), ventricular dysfunction, conduction defects and arrhythmias, residual shunts, regurgitant or stenotic valves, and aneurysms (2). As poor general health is also a risk factor, it is important to evaluate chronic cardiac (i.e., hypertension and coronary artery disease) or noncardiac coexisting diseases (i.e., diabetes) and/or complications of ACHD such as erythrocytosis, developmental and central nervous system disorders (seizures, previous ischemic/embolic events, and intracerebral abscesses), chronic lung disease, cholelithiasis, renal dysfunction, and nephrolithiasis (25–28).

Investigations

In addition to assessing the anatomy, investigations are helpful in the evaluation of the patient’s functional class and ventricular performance. Patients may undergo exercise testing, Holter monitoring, and/or electrophysiologic studies. Both transthoracic and/or transesophageal echocardiography (TEE) and cardiac magnetic resonance imaging (MRI) are relatively noninvasive and are well suited to serial follow-up assessments. MRI may be the preferred technique for the assessing right ventricular (RV) volumes and the degree of pulmonary regurgitation (PR) as well as for viewing both the right ventricular outflow tract and the proximal pulmonary arteries (23,29). In coarctation of the aorta, MRI provides optimal visualization of the entire aorta to enable the identification of residual or recurrent coarctation as well as the formation of aneurysms of the aortic root or the site of pervious surgical repair (13). MRI research tools such as the assessment of ventricular mass, vector change, and contractile geometry are likely to find clinical utility in ACHD (23).

Cardiac catheterization is helpful: (i) in the investigation into pulmonary vascular disease and the determination of its responsiveness to oxygen and vasodilators, (ii) in the assessment of functional suitability for Fontan completion, (iii) as a supplement to echocardiography and MRI in the delineation of complex congenital lesions, (iv) in the assessment of the coronary arteries, and (v) for catheter interventional procedures.

Arrhythmias

In ACHD, the congenital anomalies themselves as well as changes attributable to chamber dilation, fibrosis, surgical incisions, and hemodynamic deterioration contribute to the development of atrial and ventricular arrhythmias (23,30). The occurrence of these arrhythmias is a poor prognostic sign. Even with a simple atrial atrial septal defect (ASD), there is an increased risk of the late onset of atrial tachyarrhythmias and atrial fibrillation with closure after the age of 40 (21). Sinus node dysfunction, poor ventricular function, and the desire for pregnancy may complicate pharmacologic
management of arrhythmias. Thus, patients with ACHD often present for procedures such as catheter ablation, open ablation (Cox Maze procedure), as well as the insertion of automated implantable cardioverter defibrillators and anti-tachycardia pacemakers. Epicardial lead placement may be required for AICDs and pacemakers as transvenous placement may be complicated by difficult venous access, unacceptable thrombosis risk, or the presence of intracardiac shunts.

**Anesthetic plan**

The optimal anesthetic plan relies upon the anesthesiologist’s ability to correctly understand the patient’s pathophysiology. Premedication should be selected carefully, and its use particularly with opioids may be risky in patients in who further hypoventilation and hypoxemia could lead to decompensation. In patients with erythrocytosis, it is advisable to maintain preoperative hydration (minimizing preoperative clear fluid fasting interval or administering preoperative intravenous fluids). Intravenous fluid administration requires vigilance to avoid systemic embolization of air bubbles. Previous cardiac and noncardiac procedures and hospital admissions may limit the availability of central and peripheral vascular access sites. Because of the variety of CHD lesions and the variations within a given type of CHD, there is no ‘one-size-fits-all’ selection of anesthetic medications. Rather, the choices must be tailored to unique features of each case. Although of considerable utility in pediatric CHD, it is important to remember that ketamine may depress ventricular function in patients with maximal sympathetic activation.

**Monitoring**

Selection of monitoring must take into account the patient’s cardiac defect and overall health status, the planned surgical or cardiac catheterization procedures, and consideration of the pros and cons of invasive monitoring. Combining this information with a preoperative examination of the patient’s pulses and four limb blood pressure measurements helps guide the placement of both noninvasive and invasive monitors.

Left upper limb blood pressures are rendered unreliable by previous subclavian flap repair of coarctation of the aorta while a Blalock Tausig shunt renders the invasive and noninvasive blood pressure diminished or unobtainable in the corresponding upper limb. Previous arterial cut down or percutaneous cannulation may result in stenosis, collateral vessels, or scar tissue formation that may impair successful access as well as reliable distal arterial pressures and waveforms. In reoperative open heart surgery, a femoral artery may be unavailable for monitoring as the surgeons may require it for femoral cardiopulmonary bypass access. In addition to intermittent arterial blood gas analysis, intraarterial monitoring facilitates a continuous assessment of hemodynamics and the alterations that result from changes in anesthetic depth and/or intravascular volume status.

A previous Fontan repair precludes central venous access to the systemic atrium and ventricle. Two-dimensional and most recently three-dimensional ultrasound visualization is valuable for preinsertion evaluation of central veins and guidance during insertion (31). Pulmonary arterial catheters are rarely used because of (i) difficult or impossible placement, (ii) risk of arrhythmias, and (iii) measurements confounded by the presence of shunts or valve regurgitation. With open heart surgery, it is common to place intrathoracic catheters into otherwise inaccessible atria (left atrial or systemic atrial lines). Intraoperative TEE (including three-dimensional TEE) can provide a continuous assessment of ventricular function, preload, and changes in valve function. In addition to its ability to guide and subsequently evaluate the surgical repair, TEE has shown utility by uncovering and assessing unexpected presurgical findings in the OR. Even routinely used monitors may have additional benefits, such as the ability of pulse oximetry to track changes in pulmonary blood flow and \( R \rightarrow L \) shunting in patients with cyanotic lesions, or limitations, such as underestimation of \( P_eCO_2 \) by end-tidal \( CO_2 \) in patients with \( R \rightarrow L \) shunts (32).

**Antibiotic prophylaxis**

In contrast to the more widespread use of antibiotic prophylaxis with many dental and surgical procedures in the past, current American Heart Association recommendations limit use to a much narrower spectrum of procedures in patients with previous endocarditis, unrepaired cyanotic CHD including those with palliative shunts and conduits, the presence of prosthetic material, or device during the first 6 months after the procedure, and residual defects at the site or adjacent to the site of a prosthetic patch or device (33). In cardiac surgery, anti-staphylococcal (typically cefazolin) surgical wound antibiotic prophylaxis remains standard practice.

**Reoperation**

With reoperation, reopening the sternum can be dangerous because of the possibility of adhesions between
Considerations for patients with cyanotic lesions

In patients with cyanotic lesions, anesthesia management is aimed at promoting pulmonary blood flow through maintaining a favorable pulmonary vascular resistance (PVR), ensuring optimal driving pressure for pulmonary perfusion (systemic arterial or venous pressure depending upon the physiology), decreasing $R \rightarrow L$ shunting through maintaining normovolemia and systemic vascular resistance, optimizing hematocrit, and modulating dynamic right ventricular outflow tract obstruction (RVOTO), if present, with $\beta$-blockers. Altering the inspired concentration of oxygen ($\text{FiO}_2$) will have little effect on peripheral oxygen saturation ($\text{SpO}_2$) while systemic vasoconstriction (phenylephrine, norepinephrine) will increase $\text{SpO}_2$ either by decreasing $R \rightarrow L$ shunting or by improving the flow through an aortopulmonary shunt or aortopulmonary collaterals. The arterial oxygen saturation is frequently improved under anesthesia in patients with cyanotic lesions as a consequence of diminished $O_2$ consumption and the resultant elevation of the mixed venous oxygen saturation. Patients with cyanotic lesions have a blunted hypoxic ventilatory response while the response to hypercapnia is preserved (32).

As pulmonary blood flow is poor, the rate of rise or fall of the partial pressure of inhalational anesthetic agents in the blood and brain is slow. Thus, inhalational induction and recovery are slower. Importantly, this also leads to difficulty in reducing inhaled anesthetic agent concentration in the event of an adverse event such as hypotension. Intravenous medications have a theoretically, but perhaps not clinically significant, more rapid onset as a consequence of $R \rightarrow L$ shunting. Conversely, the onset of intravenous medications may be slowed in the presence of reduced cardiac output. Anesthetic-induced hypotension may be more profound in patients on diuretics and angiotensin-converting enzyme inhibitors.

Patients with cyanotic lesions are at additional risk of ventricular dysfunction and myocardial ischemia, as consequences of impaired oxygen transport, decreased diastolic perfusion pressure caused by shunts or collaterals, and from impaired, or occluded myocardial microvascular perfusion as a result of erythrocytosis and hyperviscosity. Chronic hyperventilation and increased hematocrit improve oxygen transport in cyanosis. Unfortunately, the increased mass and stiffness of the red blood cells (RBC) result in elevated viscosity that further increases cardiac work in hearts already compromised by chronic hypoxia-induced systolic and diastolic dysfunction. Erythrocytosis in the presence of iron deficiency results in poorly deformable RBCs that raise the risk of thrombosis (34).

Coagulation anomalies found in patients with cyanotic lesions include abnormal platelet function, diminished platelet survival because of peripheral consumption, reduced levels of vitamin K-dependent coagulation factors as well as factor V and von Willebrand factor (34). Erythrocytosis not only elevates INR and PTT but may interfere with the standard laboratory tests used to measure these indices.

Considerations for patients with pulmonary hypertension

In PHT, PVR increases as a result of changes in the pulmonary vascular bed as a consequence of being subjected to increased pulmonary blood flow and near systemic blood pressure. Initially, reactive and reversible, these changes eventually become fixed and permanent. Pathological examination reveals media hypertrophy in small muscular arteries and arterioles, cellular proliferation in the intima, migration of smooth muscle cells into the subendothelium, and ultimately progressive fibrosis leading to obliteration of these vessels. The reactive nature of PHT is characterized by exaggerated responses to sympathetic stimuli (i.e., pain or surgical stress response), acidosis, hypercarbia, hypoxia, and hypothermia. Although it may be easier and preferable to prevent exacerbations of PHT than it is to treat them, the strategies used are similar. It is advisable to use a high $\text{FiO}_2$ accompanied by hyperventilation obtained with the minimal possible intrathoracic pressure (goal $P_a\text{CO}_2$ of 25–30 mmHg and $\text{pH} > 7.45$). One must aim for an anesthetic depth that will blunt the sympathetic response as best as possible. The choice of anesthetic medication used to achieve this goal will depend upon the particular circumstances, but opioids (sufentanil, fentanyl, and remifentanil) are often helpful. Inotropic support with $\beta$-adrenergic agents (dobutamine or isoproterenol) or phosphodiesterase-3 inhibitors (milrinone) may permit the patient to tolerate this depth of anesthesia and help the RV to cope. However, one must beware of the systemic hypotension that may accompany their use and aggravate $R \rightarrow L$ shunting. Systemic vasoconstriction...
with norepinephrine or phenylephrine may be essential to increase coronary perfusion pressure, relieve subendocardial ischemia and improve ventricular function. Selective pulmonary vasodilation with inhaled nitric oxide is a mainstay of current therapy, although aerosolized prostanoids have also been used with success. Oral sildenafil, cGMP-specific phosphodiesterase type 5 inhibitor, has been used for both prophylactic and maintenance therapy. The use of other vasodilating medications has been limited by their systemic vasodilating properties.

**Additional considerations for patients with Eisenmenger’s Syndrome**

Patients with long-standing untreated L → R intracardiac or extracardiac shunts may progress to Eisenmenger’s syndrome with severe, fixed PHT with equalization of the RV and left ventricular (LV) pressures, bidirectional or even reversed (R → L) shunting and eventual dilation, and failure of the RV accompanied by tricuspid regurgitation. The physiological trespass of anesthesia and surgery can easily upset the precarious balance of systemic, pulmonary, and myocardial perfusions and lead to cardiovascular collapse in patients with Eisenmenger’s syndrome. Avoidable noncardiac surgery should not be undertaken and referral to the expertise, and resources of a specialist ACHD center should be strongly considered. In addition to sildenafil, these patients are often managed with Bosentan, a dual endothelin receptor A and B antagonist. The continuous infusion of prostacyclin analogs is also utilized, but carries thrombotic, embolic, and infectious risks as well as the potential for rebound PHT. As Eisenmenger’s syndrome carries a high mortality (40% prior to age 25 with a median survival in the mid-4th decade) and a markedly increased to prohibitive anesthetic risk, it is hoped that this condition will become increasingly rare with time (35).

**Considerations for patients with impaired ventricular function**

Impaired ventricular function is common in ACHD (36). In the absence of surgical correction or as a consequence of residual lesions, ventricular remodeling such as concentric hypertrophy and spherical dilation worsens over time. In general, pressure overload is less well tolerated than volume overload. This is common in lesions in which a morphologically right ventricle must function as the systemic ventricle.

**Additional considerations in tetralogy of fallot survivors**

Infant repair of tetralogy of Fallot (TOF) illustrates the evolution in the management of a more common lesion. In comparison with initial Blalock Taussig shunt palliation followed by late repair, infant TOF repair resolves cyanosis, circumvents dysfunctional RV remodeling, facilitates growth of the pulmonary vasculature, and may decrease the incidence of aortic root dilatation (37,38). Unfortunately, the need for transannular patching to relieve RVOTO produces chronic PR, which in turn leads to progressive RV enlargement and dysfunction, potential secondary tricuspid regurgitation, worsening exercise intolerance, heart failure, supraventricular and ventricular tachyarrhythmias, and sudden death (39–41). A mean QRS duration in excess of 180 ms is associated with an increased risk of sudden cardiac death (42). Patients may remain unaware of their symptoms until the onset of advanced ventricular dysfunction at which time concomitant LV dysfunction becomes common (29). The timing of pulmonary valve replacement was often delayed because of the commitment for subsequent replacement of the bioprosthetic valve every 10 years. Unfortunately, delayed surgical correction of PR is associated with a lack of improvement in RV function (43). It is hoped that repairs that preserve pulmonary valve function when possible, as well as undertaking early pulmonary valve replacement, may further improve TOF outcome (43,44). Anti-arrhythmia procedures at the time of pulmonary valve replacement show promise (45).

**Additional considerations for Fontan patients**

Survival following Fontan has improved to over 85% at 10 years and 80% at 15–20 years (46) (15-O) Arrhythmias, ventricular failure, and thromboembolic events are the most common etiologies of late death in Fontan patients. Tachycardia and loss of sinus rhythm are poorly tolerated in single-ventricle physiology and should be rectified promptly with due concern for the presence of thrombus. Sinus node dysfunction may lead to permanent pacing in up to 40% of Fontan patients.

Pulmonary thromboembolism may result from sluggish flow in the Fontan pathway, the presence of intravascular prosthetic material, coagulation abnormalities, and arrhythmias. Systemic thromboembolism may occur through a Fontan fenestration or residual ASD, or may originate from a ligated pulmonary artery stump, or systemic heart chamber. Oxygen
desaturations below 94% may be indicative of $R \rightarrow L$ shunting through collaterals or arteriovenous malformations, residual ASDs, or Fontan fenestrations. Progressive ventricular dysfunction with or without AV valve regurgitation is common.

Fontan patients who develop protein-losing enteropathy (PLE) have a 50% 5-year survival. Features of PLE include peripheral edema, ascites, pleural and pericardial effusions, chronic diarrhea, and an alpha-1 antitrypsin level. PLE responds poorly to medical therapy with diuretics and aldosterone antagonists, but may occasionally respond to the lowering of systemic venous pressure and improved cardiac output permitted by conversion to a fenestrated Fontan or to revision surgery in the presence of Fontan obstruction. Chronic systemic venous hypertension may lead to hepatic dysfunction and eventual cirrhosis.

**Considerations in pregnancy**

Contraceptive counseling is essential in ACHD. Thirteen percent of 599 pregnancies in a series of 562 patients with ACHD resulted in pulmonary edema, arrhythmia, stroke, or cardiac death (47). Management of pregnancy in patients with moderate to severe ACHD requires a multidisciplinary team. The normal physiological changes of pregnancy [50% increase in blood volume; 50%, 30–40% increase in cardiac output; 30% increase in heart rate and decreased systemic vascular resistance (SVR)] may lead to pulmonary overload in patients with $L \rightarrow R$ shunts and to increased shunting and cyanosis in $R \rightarrow L$ shunts. Maternal adaptation to the postpartum physiological changes also carries a particularly high mortality risk. Risk factors for elevated maternal morbidity and mortality include the following: cyanosis, PHT, poor functional status and/or heart failure (baseline NYHA class >II or EF < 40%), poor arrhythmia control, LV obstructive lesions (mitral valve area < 2 cm², aortic valve area < 1.5 cm², or peak left ventricular outflow tract gradient > 30 mmHg by echocardiography), and prior cerebral ischemic events. Maternal mortality in the presence of PHT (i.e., Eisenmenger’s syndrome) is estimated at between 30% and 70%. The normal physiological adaptation to pregnancy is altered with coarctation of the aorta with an increased heart rate being necessary to support most of the increase in cardiac output. Complications (ventricular failure, dysrhythmias, endocarditis, aortic dissection, and thromboses) may arise in almost one-third of pregnant ACHD patients with coarctation of the aorta.

In pregnant ACHD patients with $L \rightarrow R$ shunts, the lower SVR with spinal or epidural analgesia or anesthesia may be beneficial. In contrast, in pregnant ACHD patients with palliative $L \rightarrow R$ shunts general anesthesia is often recommended as it is essential to avoid dropping the SVR. Risks of pregnancy in Fontan patients include systemic venous congestion and ascites, worsening ventricular function, aggravation of AV valve regurgitation, atrial arrhythmias, thromboemboli, paradoxical emboli, spontaneous abortion, intrauterine growth retardation, and preterm birth.

Neonatal complications occur in 20% of pregnancies with prematurity and intrauterine growth retardation being most common. The incidence of CHD among the newborns was 7%. Predictors of neonatal complications included the following: cyanosis, NYHA class >II, maternal left heart obstruction, smoking, multiple gestation, and anticoagulants use during pregnancy.

**A model of care for complex ACHD**

Following the Bethesda Conference, there have been additional calls for consolidation of the care of complex ACHD into regional centers that serve a catchment population of approximately 5–10 million persons (6,7,20,23). This concentration of services can create the critical mass required to develop a team that also includes cardiologists, surgeons, anesthesiologists, intensive care physicians, radiologists, nurses, perfusionists, social workers, and other health care workers with expertise in the care and management of ACHD. This expertise ensures the provision of (i) comprehensive diagnostic services (including echocardiography, cardiac catheterization, electrophysiological testing, cardiac MRI and CT, cardiac and pulmonary exercise testing), (ii) electrophysiological interventions (ablative, pacing, and implanted defibrillator therapies), (iii) interventional cardiac catheterization procedures, (iv) critical care (including extracorporeal life support, ventricular assist device and artificial heart programs), (v) a transplantation program, and (vi) clinical and basic science research. Patients with bicuspid aortic valves, small aterioventricular septal defects, repaired ASDs, and mild pulmonary stenosis may be readily cared for in peripheral hospitals. The complex ACHD center needs readily available good communications to and from these hospitals and their physicians in its catchment region. This can be enhanced by multidisciplinary videoconferences that facilitate regularly scheduled case referral and quality improvement discussions. Ideally, such a system requires the support of those funding the health care system, as well as national specialty societies and patient interest groups.

As the evolution in ACHD care continues, will ideal anesthetic care of these adults be in the domain and
comfort zone of pediatric cardiac anesthesiologists or in the practice realm of adult cardiac anesthesiologists? It has been recommended that patients with moderate or complex ACHD (especially those with significant risk factors such as poor functional class, PHT, cyanosis or heart failure) undergoing planned complex non-cardiac surgery should be managed at the dedicated ACHD center (4,48). To meet the future demands of patients with ACHD, it is possible that there will be a need to follow the examples of other specialties and institute formalized training of those who provide anesthetic care for both their cardiac and noncardiac procedures.

References


Introduction

Congenital heart disease is the commonest birth defect, occurring in approximately one in 125 live births. Extracardiac anomalies requiring surgery within the first year of life are present in 30% (1,2). Advances in medical care have resulted in 90% of children with heart disease surviving to adulthood (3,4). These children present needing both elective and emergency anesthesia because they are subject to the same childhood ailments as other children. Some have mild heart disease with no complications, whereas others have complex disease with multiorgan dysfunction (5,6).

Children with heart disease undergoing noncardiac surgery are at an increased risk of perioperative morbidity and mortality compared with other children (7–12). These children pose a serious challenge for anesthesia. Ramamoorthy et al. (10) reviewed anesthesia-related pediatric cardiac arrests. In children with heart disease, the majority of cardiac arrests occurred during noncardiac surgery; 75% were under 2 years old, and 75% of deaths were accounted for by three distinct defects: aortic stenosis, cardiomyopathy, and single ventricle lesions. Torres et al. (9) report a 19% mortality in children with hypoplastic left heart syndrome (HLHS) <2 years old presenting for noncardiac surgery. Perioperative intensive care support is needed by 67% of children with cardiomyopathy (11). However, despite these challenges, neonates with complex disease requiring major surgery can tolerate general anesthesia with few complications (13).

Aims and limitations

This narrative review aims to discuss the literature concerning different anesthetic techniques, the major long-term complications of heart disease and suggest an evidence-based approach to managing these chil-
Managing children for noncardiac surgery

First, few studies exist evaluating anesthetic techniques in children with heart disease undergoing noncardiac surgery. Most data come from cardiac catheterization. Surgery involving major fluid shifts, changes in position (prone or Trendelenburg) or changes in intracavity pressure (laparoscopic techniques) may produce important hemodynamic and pulmonary effects that alter risk. Studies in these situations are nonexistent. Therefore, claims of efficacy and safety must be interpreted cautiously. Small case series and isolated case reports do exist and are discussed. Secondly, in a rapidly advancing field such as cardiac surgery, studies of long-term complications may reflect outdated treatment strategies. This makes application to current practice difficult. Thirdly, because of the varied and complex nature of pediatric heart disease, a ‘one-size-fits-all’ approach to management is impossible. Therefore, the approach presented here is general rather than specific and based on evidence as well as physiology.

Anesthetic techniques

The two most studied induction agents in children with heart disease for noncardiac surgery are ketamine and propofol. In children undergoing cardiac catheterization, propofol decreased systemic vascular resistance (SVR) and mean arterial pressure (MAP) (14). Heart rate, pulmonary arterial pressure (PAP), and pulmonary vascular resistance (PVR) were unchanged. In children with shunt, left-to-right flow decreases and right-to-left flow increases causing a clinically relevant reduction in oxygen saturation. Oklu et al. (15) compared propofol with ketamine. Propofol decreased both MAP and SVR, whereas ketamine increased MAP with no effect on SVR. Neither drug had any effect on PAP or PVR. Ketamine is also well tolerated in children with pulmonary hypertension (PHT) (16,17). In a review of 18 neonates with complex cardiac defects undergoing major general surgery, ketamine was the commonest induction agent in those not intubated at the time of surgery (13). Thiopentone, etomidate, and sevoflurane use is also reported for the induction of anesthesia (18–25). These reports cover a wide range of cardiac conditions including single ventricle lesions and encompass a variety of procedures from trachea-oesophageal fistula repair to laparoscopic surgery. Etomidate causes minimal hemodynamic disturbances in children with shunt lesions undergoing cardiac catheterization (26). However, the adrenal suppressive effects of etomidate are well described in adults (27,28) and in children with sepsis (29). The use of numerous muscle relaxants (suxamethonium, vecuronium, rocuronium, and pancuronium) and volatile agents are also described (18–25,30).

Isoflurane, sevoflurane, and fentanyl/midazolam infusions for maintenance of anesthesia have been evaluated during cardiac catheterization (30), or prior to cardiac surgery (31,32). In children with shunt, neither isoflurane, sevoflurane nor fentanyl/midazolam have any effect on shunt fraction (31). In children with single ventricle lesions, neither sevoflurane nor fentanyl/midazolam have any effect on myocardial contractility (30). In contrast, Rivenes et al. (32) report fentanyl/midazolam reduces cardiac index and contractility. Rivenes’s study used a heterogeneous group of children and so should be interpreted cautiously as different lesions may produce different pharmacodynamics. Hannon et al. (33) reported sevoflurane and isoflurane have a greater depressive effect on myocardial contractility in ferrets with a pulmonary artery band than in unbanded animals. In several large cases series of high-risk children for noncardiac surgery, maintenance with isoflurane and sevoflurane is described (13,18,20,34). The evidence cannot recommend one agent over another but suggests isoflurane and sevoflurane are routinely used, whereas desflurane and propofol infusions are not.

Postoperative analgesia depends on the type of surgery. For major surgery, intravenous opioid infusions are commonly used (13). Regional techniques have been used but reports are rare. Sacrista et al. (35) describe spinal anesthesia alone in an infant with HLHS undergoing colostomy formation for anorectal atresia. The spinal block was measured to the 4th thoracic vertebra level with no adverse hemodynamic effects. High spinal blocks are well tolerated in healthy children and are not associated with the reductions in MAP and heart rate seen in adults (36,37). Epidural with general anesthesia is reported in neonates with complex cardiac defects undergoing general surgery (13). Epidural infusions of ropivacaine were used and managed in a non-ICU environment with no complications reported. A recent review cites ropivacaine as having the greatest margin of safety of all long-acting local anesthetics (38).

In summary, many different anesthetic techniques have been described. Propofol dramatically reduces SVR, whereas ketamine has no effect, making ketamine the agent of choice when a reduction in SVR is undesirable or in children with PHT (14–17). Isoflurane and sevoflurane have minimal effect on myocardial contractility or shunt fraction and their use is widely reported for the maintenance of anesthesia.
The effects of desflurane and propofol infusions are unknown in this patient group. Opioid infusions, spinal and epidural anesthesia have all been used effectively (13,35).

Four major complications of heart disease in children

Arrhythmias
Some cardiac operations are associated with an increased risk of late-onset arrhythmias. Surgery involving extensive atrial sutures or ventriculotomy poses the highest risk. Arrhythmias can occur years later and be asymptomatic or associated with hemodynamic collapse and sudden death. Necrosis and progressive fibrosis extending into the conduction system are thought to be the causes (39,40).

Atrial arrhythmias are commonest after repair of sinus venous defects, atrial septal defects, atrial switch procedures (Mustard or Senning), and total cavopulmonary anastomosis (Fontan procedure). Damage to the atroventricular (AV) node and Bundle of His is commonest after ventriculotomy or right ventricle to pulmonary artery conduit (39,40). Table 1 summarizes the evidence. However, these data need to be interpreted cautiously, because modern surgical techniques and trends toward earlier repair in infancy may reduce but not eliminate these risks (41–45).

Some children with heart disease have a primary malignant arrhythmia. Prolongation of the QT interval is associated with torsades de pointes especially in children with long QT syndromes. Optimal anesthesia for these children is not well described. The evidence suggests propofol and sevoflurane (55,56) have minimal effect on the QTc interval (QT interval corrected for heart rate), whereas desflurane is known to prolong QTc in normal children (57). All children with heart disease should have a preoperative electrocardiogram (ECG). Ventricular ectopics (VE) are an ominous sign as 30% of these patients eventually die suddenly (42).

Cardiac failure
Cardiac failure is the end result of a continually volume- or pressure-overloaded heart. Limited cardiac reserve describes the situation where the heart is functioning at near maximal capacity even while the child is resting (39). Children with limited cardiac reserve must be identified because they are at high risk of cardiac failure during anesthesia. Plasma noradrenaline levels are increased in children with cardiac failure (58), and anesthetics that reduce sympathetic tone may precipitate severe cardiac failure. In this situation, propofol can have a profoundly deleterious effect on cardiac output, whereas ketamine has minimal effect (14,15). Both inhalational and intravenous inductions are prolonged, so patience is required to prevent excessive drug administration. The use of vasoactive agents and invasive monitoring may be needed even for minor surgery. Depending on the cause of cardiac failure and the risk of poor coronary perfusion, epinephrine and a vasoconstrictor such as phenylephrine should be immediately available. Major surgery involving significant blood loss and/or fluid shifts poses high risk, and full pediatric intensive care support should be available (11). Further management of children with cardiac failure is discussed elsewhere in this supplement.

Pulmonary hypertension (PHT)
PHT is defined as having a mean PAP above 25 mmHg at rest or 30 mmHg on exercise (59,60). Children at high risk are those with (i) excessive pulmonary blood flow (PBF) (left-to-right shunt) or (ii) prolonged pulmonary venous obstruction or high left atrial pressure.
Documented PHT is a clear predictor of perioperative morbidity (12,34,61). Children with suprasystemic PAP are eight times more likely to experience a major complication than those with subsystemic PAP (61). Treatment with 100% oxygen, inhaled nitric oxide, intravenous prostacyclin, inotropic support of the right ventricle, and other measures to maintain cardiac output and PBF may all be required. Therefore, full pediatric intensive care facilities should be available. Children with PHT also have reduced pulmonary compliance and increased airway resistance causing increased work of breathing (62,63). Therefore, respiratory tract infections may be poorly tolerated and have a greater impact on PVR than ordinarily expected.

PHT develops rapidly in association with specific lesions (AVSD, TA, D-TGA with VSD) and in certain patient populations (Down’s Syndrome) (64). It causes fixed structural changes in the vascular bed but with reactive vascular smooth muscle affected by several factors. Acidosis, hypercarbia, hypoxia, hypothermia, increased sympathetic stimulation, and increased airway pressure all increase PVR (65). Hydrogen ion concentration actually exerts a greater effect than carbon dioxide concentration (66). Appropriate management of these variables reduces PVR, improves RV function, and minimizes right-to-left shunting.

The anesthetic management of children (67) and adults (68) with PHT has been recently reviewed. The importance of understanding the specific intracardiac anatomy and the physiological consequences of changes in PVR, SVR, and shunt flow cannot be over emphasized. Different situations require different strategies. If in doubt, advice from a pediatric cardiac anesthetist and/or pediatric cardiologist should be sought before proceeding.

Cyanosis

Cyanosis is a common feature of unrepaired or partially palliated congenital heart disease. It is usually the result of decreased PBF and right-to-left shunting but children with increased PBF can also suffer from cyanosis. Children with cyanosis often have concurrent cardiac failure, PHT, and arrhythmias making them a high-risk group. Chronic cyanosis affects most major organ systems in the body but this discussion focuses primarily on the hematomatological consequences.

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Hypoxia causes an increase in erythropoietin thereby increasing hematocrit, hemoglobin, and viscosity (69). This allows increased oxygen delivery without a sustained increase in cardiac output. However, if hematocrit levels exceed 65%, oxygen delivery can actually be reduced, especially if iron deficiency is present because of red cell rigidity (70). Hyperviscosity is associated with cerebral vein and sinus thrombosis resulting in stroke. Children under 5 years are at highest risk especially in the presence of dehydration, fever, or iron deficiency (71,72). All children with cyanosis should have hemoglobin and hematocrit measured and preoperative fasting kept to a minimum. Hemoglobin greater than 18 g dl⁻¹ (or hematocrit >60%) is considered by some as an indication for preoperative intravenous fluid therapy in order to minimize risk.

Abnormal laboratory tests of hemostasis are present in 20% of children with cyanosis (73). They correlate with the degree of cyanosis but the etiology is unknown. Prolongation of prothrombin time or partial thromboplastin time is the commonest abnormality. Others include thrombocytopenia, platelet dysfunction, hypofibrinogenemigena, and accelerated fibrinolysis (74). Even when coagulation tests are normal and children are asymptomatic, the risk of excessive postoperative bleeding is still real. All cyanotic children should be assumed at risk. If a child is receiving aspirin therapy to maintain shunt patency, the risk of shunt thrombosis is usually greater than that of bleeding, so aspirin therapy should continue. Also, as the effects of aspirin last many days, discontinuing the drug immediately before surgery has little effect.

Animal models show reduced ability to increase cardiac output in response to increased demands (75,76). Therefore, premedication is commonly used to minimize distress on induction. In children with right-to-left shunts, end tidal carbon dioxide (CO₂) monitoring underestimates arterial CO₂ (77). Profound hypoxia can also occur, especially in conjunction with respiratory depressants such as opioids, because the hypoxic ventilatory response is blunted (78). So, careful postoperative monitoring including oxygen saturation is recommended (39,79).

Approach to preoperative assessment and anesthetic management

Children with heart disease presenting for noncardiac surgery are at increased risk of perioperative morbidity and mortality. Table 2 summarizes the children at highest risk (7–12). No data exist on patient outcome or satisfaction regarding anesthetizing these children in their local hospital or moving them to an expert center. In Slater et al.’s series (18) of laparoscopic surgery in neonates with HLHS, all were anesthetized by a pediatric cardiac anesthetist. Conversely, in Walker et al.’s series (13) of major general surgery in neonates with complex cardiac defects, not all infants were
anesthetized by specialist cardiac anesthetists, but full cardiology, cardiac anesthesia, and intensive care support were available. Professional responsibility dictates that the anesthetist must understand the cardiac anatomy and physiology. Depending on the lesion, this includes ‘balanced’ (parallel) and single ventricle physiology; factors affecting SVR, PVR, and shunt flow including anesthetic drugs and ventilator settings. These are outlined in more detail elsewhere (39,40,79).

Given that high-risk children are likely to require specialist support and have increased perioperative morbidity (7–12), an evidence-based approach suggests all high-risk children are anesthetized where specialist facilities are available. However, this may not be feasible in every situation especially those children presenting for emergency surgery. In such situations, good early communication and co-operation is essential. The local hospital should telephone the specialist center for advice, and where possible think about early transfer for any high-risk child who may require surgery. Specialist centers should realize their responsibilities and facilitate the transfer of such children.

Meticulous preoperative preparation involves (i) routine anesthetic history and examination; (ii) evaluation of long-term complications (anesthetic implications are discussed earlier), and other features that put children in a high-risk category (see Table 1); (iii) finally, specific attention to the following areas that are easily overlooked:

Respiratory: Respiratory tract infections have a greater impact on PVR than expected in children with PHT or cavopulmonary anastomosis (62,63). Oxygen saturations compared with predicted values for the specific defect give an indication of the amount of PBF, which in turn influences the risks of PHT, right ventricular failure, and cyanosis.

Cardiovascular: Features of arrhythmias, cardiac failure, and PHT should be sought. Review previous echocardiography and cardiac catheterization reports (these may need repeating if the child has ongoing symptoms and/or is under active cardiology follow-up); perform preoperative ECG in those at risk. Examination of peripheral and central veins gives forewarning of cannulation difficulties and may influence anesthetic technique.

Drug history: Many children receive numerous medications such as aspirin diuretics, angiotensin converting enzyme (ACE) inhibitors, and anti-arrhythmics. Cardiac medications are not associated with clinically important electrolyte disturbances, so routine preoperative electrolyte testing is unnecessary (80). Generally, all cardiac medications should be given on the morning of surgery (40). However, some anesthetists prefer to omit ACE inhibitors based on studies of adults with ischemic heart disease and hypertension; in which hypotension on induction of anesthesia is reported (81–83), although other adult work dismisses these claims (81,84,85). Data in children are lacking. Aspirin therapy to prevent shunt thrombosis should usually be continued. Children on warfarin therapy need to be admitted to hospital for anticoagulant monitoring and establishment on intravenous heparin prior to surgery.

Premedication: Commonly used to avoid distress, minimize oxygen consumption, and may reduce the amount of induction agent required so minimizing reductions in SVR. Cyanotic children and those with heart failure will require monitoring of vital signs after administration and may require oxygen therapy to maintain oxygen saturations.

Endocarditis prophylaxis: Appropriate guidelines must be followed (86,87).

Communication: Good communication between all health care professionals, the child, and their family is important including discussion of associated risks.

Conclusions

Children with heart disease are at increased risk of perioperative complications. The cardiovascular anatomy and physiology is complex and each case requires individual evaluation of risk factors. With the exception of ketamine for children with PHT or where reducing SVR is deleterious, there is no evidence to recommend one anesthetic technique in favor of another. There is no evidence of patient outcome or satisfaction regarding treatment in the local hospital or expert center. However, high-risk children are likely to require specialist support, so these facilities should be available where possible.
Managing children for noncardiac surgery

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Introduction

Bleeding remains a major clinical problem during and after pediatric heart surgery. Young age, low weight, use of deep hypothermia, high preoperative hematocrit, and complex surgery are risk factors for severe bleeding (1–3). Bleeding occurs because of surgical trauma leading to opening of blood vessels; all bleeding is ‘surgical bleeding’. However, achieving acceptable hemostasis is often complicated by the presence of coagulopathy. The principle causes of coagulopathy are discussed to provide a context for treatment. The role of laboratory and point of care tests, which aim to identify the cause of bleeding in the individual patient, is also discussed. An attempt is made to examine the current evidence for available therapies, including use of blood products and, more recently proposed, approaches based on human or recombinant factor concentrates.

Models of coagulation

Traditional models of coagulation have presented coagulation as a linear cascade of proteolytic enzymes. The implication has been that each step is necessary and of equal importance. More recent descriptive models of coagulation have stressed the importance of platelet and cellular elements (such as white cells and endothelium) and have recognized that coagulation occurs not as a linear process but as a complex web of interactions between procoagulant factors, inhibitors, and the fibrinolytic system (Figure 1) (4). This distinction has clinical relevance in explaining the observations that functionally normal coagulation can exist despite low levels of clotting proteins (in neonates and moderate liver dysfunction) (5), that deficits in one part of coagulation can be compensated for by other parts of coagulation (use of fibrinogen to correct for thrombocytopenia (6) or use of activated factor VIIa in hemophilia), and questions some approaches to acquired bleeding (use of laboratory coagulation tests (5) and some use of fresh frozen plasma). A difficulty
Coagulopathy and cardiac bypass

In the absence of anticoagulants, blood will clot in extracorporeal circuits. This has been ascribed to the activation of the ‘intrinsic’ pathway involving prekallikrein and factor XII upon contact with the artificial surface. However, patients deficient in factor XII or prekallikrein clot at the same rate as other patients, and the ‘intrinsic’ pathway appears to play little role either in normal coagulation or in clotting inside extracorporeal circuits (7,8). The lining of artificial circuits differs from endothelium in two respects: proteins will bind freely to their surface and they lack any inhibitory effect on coagulation. Binding of fibrinogen (together with fibronectin and von Willebrand factor) leads to adherence of white cells, red cells, and platelets (7). The adherent platelets undergo activation encouraging further adhesion, releasing procoagulants, and presenting a large phospholipid surface upon which further activation occurs. Adherent monocytes express tissue factor allowing coagulation to proceed as described previously. While heparin dramatically reduces thrombin formation and the formation of fibrin clots, it is an imperfect anticoagulant and does not prevent initial protein binding or activation of coagulation or platelets. This leads to defects in platelet numbers, in function of platelets, in fibrinogen concentration, and in the activation of fibrinolytic systems. Activation of fibrinolysis will lead to dissolution of clots, further reduction in platelet function, and increased concentrations of fibrin degradation products, which inhibit coagulation further (9).

Figure 2 A normal thromboelastogram (TEG) trace is shown. The output of TEG is graphical; however, a number of numerical values can be derived to describe the curve. R-time is the time from beginning the sample until the amplitude of the trace reaches 1 mm; it describes the initiation of clotting. Maximum amplitude (MA) is the largest amplitude reached; it describes the strength of the clot formed. The α angle describes the steepness of the initial part of the curve; this is often referred to as the ‘clot kinetics’. Lys 30 is the ratio of the amplitude of the trace 30 min after the maximum amplitude to the maximum amplitude; this describes the stability of the clot.

Figure 1 This figure demonstrates the major pathways involved in normal coagulation. Coagulation is initiated by leakage of factor VIIa and platelets from traumatized blood vessels. When platelets come into contact with von Willebrand factor (VWF) and collagen, they undergo a process of activation, which includes the release of procoagulants, a dramatic increase in surface area and expression of adhesion molecules (for other platelets and fibrin). Factor VIIa, usually present in low concentrations within blood vessels, makes contact with tissue factor (TF) bound to cells (principally fibroblasts but subsequently white cells). This leads to the production of a small quantity of thrombin, which initiates a positive feedback loop (involving a number of factors, further conversion of factor VII to VIIa and activation of platelets) producing large quantities of thrombin. This leads to the production of fibrin (from fibrinogen), which together with activated platelets forms clot. The major inhibitor is the Protein C (PC) system, which inactivates factor VIII and V. In the absence of endothelium bound thrombomodulin (TM) (for example in invitro blood tests), little active protein C is produced. Subsequent stabilization of the clot by factor XIII, inhibitors other than protein C, and the fibrinolytic system are not shown for simplicity.
As well as the effects of interaction between blood and extracorporeal surfaces, other factors will add to coagulation anomalies. Blood split into the pericardial space and returned via ‘pump’ suction is a further (and possibly more important) cause of activation (10). Clotting factors and platelets will undergo dilution on initiating bypass (11,12), red cells and platelets may be damaged from suction, bleeding itself may add to coagulation abnormalities, extensive surgical dissection will add to bleeding, and many patients will have pre-existing coagulation abnormalities because of cyanotic heart disease (13–15), critical illness, or medications.

Monitoring of coagulation

Tests of coagulation are performed with the aim of identifying the coagulation abnormalities most likely to be contributing to bleeding. If results from these tests can be reported to the clinician in a short time, therapy can be directed more effectively at the specific cause of bleeding, leading to both more rapid correction of coagulopathy and avoiding unnecessary therapy. Tests can be divided between those conducted primarily in hematology laboratories and those available at the patient’s bedside (point of care devices). The objective in using point of care tests is to make the results available to clinicians more rapidly; though, as the tests available are also different, they will have their own advantages and limitations.

Laboratory-based coagulation tests

The most commonly performed laboratory tests relevant to coagulation are the full blood count (to give platelet concentration) and clotting studies [prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time, and fibrinogen concentration]. Clotting studies are performed using patient’s plasma and so are insensitive to effects owing to abnormalities of platelets or cellular elements. Citrated plasma is mixed with an excess of calcium and a reagent. Use of different reagents aims to test different parts of the coagulation pathway. The two most important tests used in acquired coagulopathy are the PT and fibrinogen concentration. PT is widely used for monitoring acquired coagulopathy in a number of situations, including postcardiac surgery. The reagent used, thromboplastin, contains tissue factor and phospholipids; activation therefore occurs by the normal ‘tissue factor’ pathway. Problems arise in the interpretation of this test for two reasons. First, PT is prolonged in a number of situations despite functionally normal coagulation, including healthy neonates and in patients with moderate hepatic disease (5). In these patients, the long PT reflects low concentrations of coagulation factors which, in vivo, are balanced by low concentrations of inhibitors. A long PT is also common in the absence of abnormal bleeding after pediatric heart surgery and this may reflect a similar situation. Secondly, deficiency of coagulation factors may not be the primary cause of bleeding. Congenital hemophilias are represented by profound deficiency of a single clotting factor. Acquired coagulopathy after surgery represents multiple coagulation defects with multiple origins. Not all these defects will be of equal importance, and correction will not have an equal impact on bleeding. After cardiac surgery, deficiencies of fibrinogen and functional platelets are likely to make a greater contribution to bleeding than deficiency of other factors (3,16,17). Basing treatment on PT may not lead to optimal correction of bleeding.

Thrombin time reflects fibrinogen activity but it is also prolonged by inhibition because of fibrinogen degradation products (FDP) or heparin. The most common method for the determination of fibrinogen concentration, the Clauss method, is derived from the thrombin time. It is not interpretable in the presence of heparin and will be inaccurate in the presence of FDPs (common after heart surgery) (18).

Point of care monitoring

Point of care monitoring of coagulation may be aimed at the control of heparin administration or at the identification of coagulopathy. Devices available for monitoring of heparin have been reviewed previously (19,20). For the purpose of this article, only the latter will be discussed. Over the last few years, improvement in design has allowed a number of devices, previously suitable only for use in laboratories, to be developed for point of care use. Devices with potential for use during cardiac surgery include point of care equivalents of laboratory tests (such as APTT and PT), thromboelastography (TEG and ROTEM), and specific tests of platelet function (Sonoclot analyzer, PFA-100 and MultiPlate platelet aggregometer) (21). Currently, only variations of thromboelastography have been widely employed and will be the focus of this discussion (22,23). The differences between the TEG and rotational thromboelastography (ROTEM) have been recently reviewed (24). While important differences exist and results from these devices are not interchangeable (25), the principle of their clinical application is similar. The discussion will focus on TEG while important differences in clinical application will be highlighted.
In conventional TEG, a pin is lowered into a cup containing whole blood. The cup is rotated in each direction approximately 4°. As the blood begins to clot, the pin will begin to move with the cup, the force of the movement being a marker of the strength of the clot at that moment in time. This force is used to construct a graph of clot strength over time. A typical (Kaolin activated) TEG is shown in Figure 1. Initially, a straight line indicates no clot being present (the pin does not move), subsequently, a clot begins to form and moves the pin to reach a maximum amplitude taken to indicate maximum clot strength. The stability of the clot is then indicated by the degree to which the clot retains this strength. An activator is usually added to the cup to speedup analysis, and other substances may also be added to modify the test. Kaolin is the most common activator used with conventional TEG, while the ROTEM is commonly performed as a battery of tests including kaolin (inTEM) and tissue factor (exTEM). A recent modification of TEG is ‘rapid’ TEG using a mixed activator aimed at giving information on clot strength more rapidly (26).

The output of the TEG is primarily graphical. To allow comparison of results and to develop protocols based on TEG, it is necessary to reduce this graphical output to numerical values (Figure 2); computerization has allowed for rapid calculation of these values. Similar values can be calculated for ROTEM although the values are not interchangeable and different nomenclature is used. Population ‘normals’ have been described for these values in adults, children (27), and children with congenital heart disease (28). Some care is required in the use of such reference values, as these will be different if different activators and additives are used. In the interpretation of unmodified TEG values, a prolonged R-time is an indication of residual anticoagulant or deficiency of clotting factors, a low maximum amplitude indicates poor clot strength, and increased degree of lysis (high Lys 30 or Lys 60) indicates the presence of fibrinolysis. Low amplitude (MA) is the TEG value most closely correlated with bleeding after heart surgery (16,23). A low MA may be the result of low platelet number, poor platelet function, low fibrinogen, poor function of fibrinogen, or a combination of these factors. Moganasundram et al. (16) demonstrated a close correlation between TEG MA and the product of platelet count and fibrinogen concentration in children. Similar findings of an interaction between platelets and fibrinogen have been confirmed in adults (29).

Adaptation of the TEG can add further information. Addition of heparinase to the cup will neutralize any effect of heparin, and comparison to an unmodified TEG will identify patients in which reversal of heparin has been inadequate. An estimate of fibrinogen activity can be made by the addition of blockers of platelet function; the resulting clot will, therefore, reflect the activity of fibrinogen alone.

Integration of monitoring into clinical care

A rational approach to bleeding after heart surgery should include a clinical assessment of bleeding at that point in time (30,31), an appreciation of risk factors, and use of specific tests to identify the presence and mechanisms of coagulopathy. In the absence of clinical bleeding, therapy is not required even if specific tests demonstrate an abnormality. In the presence of bleeding, tests can help to differentiate the specific cause. The most common causes of bleeding immediately after bypass are surgical causes, platelet abnormalities, fibrinogen insufficiency, inadequate reversal of heparin, and combinations of these factors (16,32). In the absence of clotting abnormalities, it is more likely that further surgical efforts will reduce bleeding than the administration of blood products and early recognition of this can lead to more appropriate treatment (33). However, in small children, this is an uncommon situation and abnormalities are likely to be present even if the primary cause of bleeding is surgical. If bleeding is persistent despite the administration of appropriate clotting factors and normalization of tests, then further surgical efforts are indicated.

Barriers exist to applying such an approach and it may not always be appropriate. Time is required to perform tests and to initiate treatment (in particular, use of blood products) and delaying treatment, while awaiting diagnostic information may be counterproductive. This can be minimized by the use of tests that will give rapid results (26) or by performing tests during bypass, which will predict coagulopathy after bypass (17). Inadequate reversal of heparin is an easily reversible cause of bleeding, which can be rapidly confirmed by point of care tests such as heparinase-modified TEG. Some patients, such as neonates undergoing complex procedures, are at very high risk of bleeding. If excessive bleeding is present, after reversal of heparin, initial empirical transfusion of platelets or cryoprecipitate is indicated (3,30) and waiting for coagulation tests may only lead to delay in treatment. If the patient fails to respond to initial treatment, the cause for ongoing bleeding is likely to be less clear and coagulation tests can help to guide further therapy. Figure 3 demonstrates the ability of TEG to follow changes in coagulation during a case.
In other situations and when bleeding is of lesser severity, greater consideration can be given to the need for treatment. Approaches to bleeding based on clinical assessment of bleeding and results of coagulation tests can avoid unnecessary transfusion. Transfusion algorithms have been introduced to this end. Traditionally, these algorithms have been based on laboratory tests (Table 1) and have been developed primarily through clinical consensus (34–36). Often the clinical evidence (for the chosen indication, the specific product, or the dose) is weak. In addition, the guidelines are frequently applied to highly heterogeneous groups of patients; it is unlikely that the same management is appropriate for an elderly adult with liver disease or a neonate undergoing heart surgery. Algorithms based on point of care monitoring have also been introduced (Table 2). These have been successful in limiting unnecessary transfusion in adults (37–39) and children (32). The algorithms introduced have largely been extrapolated from laboratory-based guidelines and may not fully exploit the advantages of tests such as thromboelastograms. Table 2 gives advice on TEG-guided transfusion. Evidence that the introduction of transfusion algorithms based on point of care monitoring can improve outcome other than reducing unnecessary transfusion is limited (40).

**Specific agents**

**Blood products**

Platelet dysfunction and thrombocytopenia are common after cardiac bypass in infants. Hence, in the presence of bleeding, transfusion of platelets is logical. Coagulation variables that relate to platelet number and function (such as TEG MA) are corrected by the infusion of platelets, and clinical experience indicates that platelet transfusion is highly efficacious at reducing bleeding. This has been confirmed in a small study of children postcardiac surgery (3). A platelet count of $<108 \times 10^9$ l$^{-1}$ has been identified as a predictor of bleeding, while clot strength measured by TEG reduces steeply at platelet counts below $120 \times 10^9$ l$^{-1}$. The cur-

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**Table 1 Guidelines for the transfusion of blood products.**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Product and dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT &gt;1.5 times control</td>
<td>FFP 10–15 ml·kg$^{-1}$</td>
</tr>
<tr>
<td>APTT &gt;2.0 times control</td>
<td>FFP 10–15 ml·kg$^{-1}$</td>
</tr>
<tr>
<td>Platelet count</td>
<td>Platelet concentrate 10 mls·kg$^{-1}$*</td>
</tr>
<tr>
<td>$&lt;50 \times 10^9–100 \times 10^9$</td>
<td></td>
</tr>
<tr>
<td>Fibrinogen $&lt;0.8–1.0$ g·l$^{-1}$</td>
<td>Cryoprecipitate 1 unit per 10 kg</td>
</tr>
</tbody>
</table>

*Platelet products will vary between institutions and local guidelines on dosage should be developed.

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**Figure 3** The ability of thromboelastogram (TEG) to follow changes in coagulation through a case is demonstrated. Dotted lines show a ‘normal’ trace. The patient was a newborn who had undergone an aortic arch repair. The baseline trace (a) demonstrates a mildly elongated R-time but is otherwise normal. After bypass platelets were administered empirically because of excessive bleeding. Bleeding continued and a TEG was performed to identify the cause of bleeding. This demonstrated a low amplitude and excess fibrinolysis (b). Tranexamic acid was given with some effect (c) followed by the infusion of cryoprecipitate (d). Following this, bleeding reduced dramatically and the TEG returned to the baseline.
rent recommendation of targeting a platelet count of approximately $100 \times 10^9 \text{ l}^{-1}$ appears reasonable. Use of platelets for initial treatment of presumed coagulopathic bleeding (in the absence of specific clotting tests) also seems reasonable.

The use of fresh frozen plasma (FFP) is based on the observation that concentration of clotting factors is often low immediately post bypass. The case for use of FFP is based on the observation that concentration of clotting factors is often low immediately post bypass. The use of fresh frozen plasma (FFP) is based on the observation that concentration of clotting factors is often low immediately post bypass. The use of fresh frozen plasma (FFP) is based on the observation that concentration of clotting factors is often low immediately post bypass. The use of fresh frozen plasma (FFP) is based on the observation that concentration of clotting factors is often low immediately post bypass. The use of fresh frozen plasma (FFP) is based on the observation that concentration of clotting factors is often low immediately post bypass. The use of fresh frozen plasma (FFP) is based on the observation that concentration of clotting factors is often low immediately post bypass. 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Table 2 Commonly measured TEG parameters, with guidance on their significance and suggested action. Thresholds for transfusion or other treatments should be seen only as a guide, and treatment should be guided by the clinical situation and known risk factors for coagulopathy. Treatment is only indicated in the presence of active bleeding

<table>
<thead>
<tr>
<th>TEG parameter</th>
<th>Additive</th>
<th>‘Normal’ value</th>
<th>Interpretation</th>
<th>Suggested action</th>
</tr>
</thead>
<tbody>
<tr>
<td>MA (kaolin)</td>
<td>Kaolin</td>
<td>54–72 mm</td>
<td>Reflects platelet number, platelet function, fibrinogen concentration and dysfunction</td>
<td>&gt;48 mm platelets or cryoprecipitates are not indicated</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;43 and if patient is bleeding, there is likely benefit from platelet or cryoprecipitate infusion</td>
</tr>
<tr>
<td>R-time (kaolin)</td>
<td>Kaolin</td>
<td>4–8 min</td>
<td>Similar to ACT is a complex parameter affected by anticoagulation, factor deficiency, and presence of inhibitors. Also operator variable</td>
<td>If long, consider residual heparin (check heparinase TEG) or factor deficiency</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>FFP may be indicated if &gt;15 min but other abnormalities should be corrected first</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>If severe bleeding and long R-time, consider use of Prothrombin Complex Concentrates</td>
</tr>
<tr>
<td>Lys 30/Lys 60</td>
<td>Kaolin</td>
<td>0–8%</td>
<td>High-level diagnostic of abnormal fibrinolysis</td>
<td>Treat with antifibrinolytic drugs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0–15%</td>
<td></td>
<td>If unmodified R-time is &gt;1.5 times heparinase-modified R-time, further protamine should be given</td>
</tr>
<tr>
<td>Heparinase-modified R-time</td>
<td>Heparinase</td>
<td>As R-time</td>
<td>Useful in heparinized patient. TEG MA on bypass shows correlation with bleeding post bypass</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>If ran together with unmodified TEG, a shorter R-time indicates residual heparin or contamination</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>‘Traditional’ management is to supplement fibrinogen until &gt;1 g l$^{-1}$ in the presence of bleeding. If active, bleeding likely to be further benefit in targeting concentration 2 g l$^{-1}$ or higher. Can be achieved with cryoprecipitate or fibrinogen concentrate</td>
</tr>
</tbody>
</table>

TEG, thromboelastogram; FFP, fresh frozen plasma.

to demonstrate benefit, although the trials examined were small and conducted in heterogeneous populations (41). In a small observational study, a number of patients had coagulopathic bleeding after transfusion of platelets; if these patients were then given FFP, bleeding increased, while if cryoprecipitate was given, bleeding improved (3). The lack of efficacy may be related to dose. FFP is frequently given in doses below the recommended dose of 10–15 ml kg$^{-1}$ (42); though, this dose may itself be inadequate to restore factor concentration. Modeling of FFP administration in major trauma suggests that much larger doses may be required to boast or retain factor levels (43). It is possible that a dose of 30–40 ml kg$^{-1}$ may be more appropriate; though, administration of such a large volume is unlikely to be desirable except in the context of massive ongoing bleeding. Dilution of platelets and red cells,
due to administration of large volumes of FFP, may in fact exacerbate bleeding. Addition of FFP to the bypass circuit may allow the administration of much larger doses, however benefit appears to be confined to smaller patients (44,45).

Not all coagulation factors are of equal importance during bleeding. Fibrinogen is normally present in much higher concentrations than other clotting factors and while other factors are mainly involved in initiating or amplifying thrombin formation, fibrinogen is a substrate for the production of fibrin. Deficiencies of fibrinogen are reflected in reduced strength of clot and are associated with increased bleeding (16). Cryoprecipitate is the most concentrated fibrinogen replacement widely available with a fibrinogen concentration 4–8 times that of FFP; though, a unit of cryoprecipitate contains less fibrinogen than a unit of FFP, and multiple units will be required in larger patients. One unit for each 10 kg should raise fibrinogen concentration by 0.5–1.0 g l⁻¹. As well as fibrinogen, cryoprecipitate is a source of Von Willibrands factor, Factors VIII and XIII, although the clinical significance of this is unclear. Cryoprecipitate has been effective in treating bleeding resistant to platelet concentrates alone during pediatric heart surgery (3).

**Human-fractionated factor concentrates**

Human-fractionated factor concentrates are produced from pooled human plasma. They undergo pasteurization, which will neutralize blood-borne viruses but (potentially) not prions. They are presented as a dried powder requiring reconstitution. They do not require cross-matching and have a long shelf life avoiding some of the logistical problems with the supply of other blood products.

Prothrombin complex concentrates (PCCs) are mixtures of inactive factor II (prothrombin), VII, IX, and X plus the coagulation inhibitors Protein S and C. A number of different brands of PCC are available, which have different relative concentrations of these factors. In some older products, low concentration of Protein S and C has been associated with increased thrombogenicity, while low concentration of factor VII has been associated with a lack of effect (46). PCCs are currently considered safe and reliable for urgent reversal of oral anticoagulants (47,48). The use of these agents in other causes of acquired coagulopathy is less certain although case series in adult patients have been encouraging (49,50). Widespread use in children after heart surgery requires more evaluation.

Fibrinogen concentrate has been available in continental Europe for over 20 years and appears to be a safe alternative to cryoprecipitate (51–53). Use in cardiac surgery in children and adults has been increasing (54,55). It is expected that this agent will be available in the United States and United Kingdom in 2010. Unlike cryoprecipitate, it contains only fibrinogen, and a direct comparison of these two agents in acquired coagulopathy has not been made. Potentially, it allows for more rapid correction of fibrinogen concentration as it will not require defrosting and can be administered in a smaller volume. Combining the availability of this agent with rapid measurement of fibrinogen concentration (using modified TEG) is an attractive approach (55–58). A small randomized study comparing prophylactic administration of fibrinogen concentrate to placebo in adult cardiac patients demonstrated a reduction in bleeding (59). Recombinant fibrinogen is currently under development but it will be several years before it is available.

The ease of administration and low volume of fibrinogen concentrates compared to FFP or cryoprecipitate can allow targeting of higher fibrinogen concentrations than have been used previously (57,60). It is possible that such use could reduce both bleeding and the need for platelet transfusion. In TEG studies, high concentrations of fibrinogen can restore clot strength despite low platelet numbers. In animal models of bleeding and thrombocytopenia, fibrinogen concentrates were superior to stored platelet concentrates in resolving bleeding (6). Such an approach requires further evaluation including the assessment of effectiveness, safety, and identification of appropriate targets.

**Recombinant factor concentrates**

Use of factor VIIa in pediatric heart patients has been previously reviewed (61). Numerous case reports have shown effectiveness in treating severe bleeding in a number of situations including pediatric heart surgery. Significant questions concerning the indication for this agent, dose, and safety remain. Prophylactic use in a relatively low dose in children was ineffective in reducing bleeding (62). In adults undergoing heart surgery, rVIIa was effective in reducing bleeding, although the rate of serious adverse effects was higher than placebo (63). Because of concern over thrombotic complications and ineffectiveness in preventing bleeding, it would be reasonable to confine use to treatment of serious life threatening bleeding.

Human and recombinant factor XIII has been described for use during heart surgery (64–66) and is supported by animal work (67). Factor XIII functions by stabilizing and strengthening bonds in the fibrin polymer and would, therefore, be expected to contri-
bute to clot strength and stability. Association between factor XIII concentration and bleeding have been inconsistent (68,69). Factor XIII also has a more general role in healing and may reduce myocardial edema and pleural effusions in children after heart surgery (70,71). The role of factor XIII replacement is uncertain; though, the development of a recombinant concentrate of this factor may lead to increased interest.

Other drugs

Treatment with antifibrinolytics such as aprotinin, tranexamic acid, or epsilon aminocaproic acid is common during pediatric heart surgery. Use of aprotinin in children has reduced dramatically because of safety concerns in adults (72–75), despite retrospective studies that show a lack of serious toxicity in children (76). Aprotinin is no longer available in many countries. Tranexamic acid and epsilon aminocaproic acid have evidence of efficacy in children although probably less than aprotinin (77–79). Only a single study has addressed dosing of tranexamic acid in children (80) and dosing remains extremely variable (abstract APA 2010).

Desmopressin increases plasma levels of von Willibrand factor with potential for reducing bleeding. In adults undergoing cardiac surgery, any benefit is confined to patients with high anticipated blood loss (81). Trials of desmopression in children and adults undergoing surgery for congenital heart disease have failed to show a beneficial effect (82–84).

Conclusion

Coagulopathy is a common cause of excess bleeding after heart surgery. Treatment should aim to reduce bleeding and should only be initiated in the presence of bleeding. ‘Traditional’ treatment using blood products is largely successful, and empirical use of these products is often appropriate, particularly in the initial treatment of severe bleeding and in high-risk patients. A strategy based on coagulation testing and application of specific therapies is likely to be more successful in patients who fail to respond to initial empirical treatment. Alternatively, in lower-risk patients, the empirical use of blood products is likely to lead to excessive transfusion, and an approach based on a clinical assessment of bleeding, an appreciation of risk factors, and use of tests is likely to reduce transfusion. Points of care tests of coagulation, in particular the TEG, have theoretical and practical advantages over laboratory-based tests.

Management of bleeding after pediatric heart surgery using strategies based on infusion of more specific factor concentrates and fibrinogen is promising. As yet, these approaches are largely untested either for efficacy or safety. Trials of therapy aimed at treatment of bleeding are challenging; though, these problems are not insurmountable and the benefits from such trials will be considerable.

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REVIEW ARTICLE

Analgesia and sedation after pediatric cardiac surgery

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General principles

Infants and children admitted to the intensive care unit (ICU) require treatment for their primary disease and maintenance of bodily functions (fluid balance, energy intake, temperature control) to optimize recovery. Additional treatments provide analgesia, reduction in conscious level and when indicated, muscle relaxation. While this triad forms the basis of classical anesthesia, in pediatric intensive care they are used for longer periods, often below the levels required for surgery and with different goals. This brings to the fore specific problems related to the drugs. These include differing pharmacokinetics and drug responses owing to age and individual pathophysiology, tolerance and withdrawal, toxicity associated with long-term use, and the need to effectively monitor drug effect against delivery. Regrettably, administration of sedative drugs in the pediatric intensive care unit (PICU) is often approached in a generic way and as an afterthought, with more attention paid to the primary disease, which can lead to avoidable morbidity.

Undersedation and oversedation are both harmful. Inadequate sedation is unacceptable in a vulnerable child who may be unable to move or communicate distress as a result of the use of muscle relaxants, while the unparalyzed child may ‘fight’ the ventilator leading to ineffective ventilation, accidental extubation, or the loss of invasive access or monitors. In intensive care, agitation and inadequate sedation has been correlated with adverse short- and longer-term outcome (1,2). Recent data has highlighted that intensive care and surgery is associated with long-term dysregulation of nociceptive mechanisms, which may change behavior and responses to future sensory and pain stimuli (3). By contrast, oversedation delays recovery, promotes tolerance to the drugs and leads to distressing symptoms on their withdrawal (agitation, seizures, hallucinations, psychosis, fever, and tachycardia) (4). Maintaining ideal analgesia while at the same time promoting earlier extubation and PICU discharge can be difficult to achieve. Infants have an almost binary state of consciousness (5), and a normally active 3-year-old cannot easily be persuaded to remain quiescent for long periods in the ICU environment using nonpharmacological comforting measures alone. Furthermore, in the current healthcare environment, there are considerable consumer/parental pressures to

Keywords
sedation; analgesia; pediatric; intensive care; cardiac; withdrawal

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Summary

In recent years, the importance of appropriate intra-operative anesthesia and analgesia during cardiac surgery has become recognized as a factor in postoperative recovery. This includes the early perioperative management of the neonate undergoing radical surgery and more recently the care surrounding fast-track and ultra fast-track surgery. However, outside these areas, relatively little attention has focused on postoperative sedation and analgesia within the pediatric intensive care unit (PICU). This reflects perceived priorities of the primary disease process over the supporting structure of PICU, with a generic approach to sedation and analgesia that can result in additional morbidities and delayed recovery. Management of the marginal patient requires optimisation of not only cardiac and other attendant pathophysiology, but also every aspect of supportive care. Individualized sedation and analgesia strategies, starting in the operating theater and continuing through to hospital discharge, need to be regarded as an important aspect of perioperative care, to speed the process of recovery.
ensure that all discomforts whether real or perceived are avoided. Recent advances in drug choices, patient monitoring, and other therapeutic options, however, offer new prospects for the future.

Simplistically, analgesic drugs should be given for pain relief, sedative drugs for reduction in conscious level, and muscle relaxants used only for specific situations when paralysis is essential (e.g. low cardiac output states, when it may be necessary to anesthetize, paralyze, and cool a child). However, there is some cross-over in these roles: morphine has sedative properties, ketamine provides analgesia and anesthesia, and even muscle relaxants may have an additive effect on reduction of conscious state through deafferentation (6). Individual drugs have secondary properties that may be exploited therapeutically in specific situations, for example the use of high-dose opioids in the management of pulmonary hypertension. Sedation and analgesia strategies need to be viewed as a collaborative effort between anesthetist and intensivist to optimize the ‘postoperative recovery gradient’ for the individual. For example, the perioperative strategy for an infant VSD may include on table or early extubation within 4 h, with continued sedation and analgesia to ensure that the infant can cope with the constraints of intensive care management. By contrast, the complex, postoperative neonate with a low cardiac output state may have an ongoing requirement for high-dose opioids, sedation, and paralysis in PICU.

Analgesia

Analgesic drugs comprise opioids, local anesthetic agents, prostaglandin synthetase inhibitors (NSAID’s), acetaminophen, ketamine, and alpha-2 agonists (clonidine and dexmedetomidine) (Table 1 and 2). Opioids remain the primary analgesic agents after cardiac surgery because of their high efficacy. Co-analgesia with NSAID’s and acetaminophen plays a key role in reducing opioid requirements and side effects (7), which is particularly useful for fast-track surgery.

Opioids have properties other than analgesia that can be exploited in the care for the critically ill child. Potent opioids such as fentanyl, sufentanil, and remifentanil delivered at doses higher than that required simply for analgesia can obtund hemodynamic and adverse hormonal and metabolic responses in the critically ill. Studies by Anand and others demonstrated that high-dose opioids used during surgery were associated with reduced stress response, nitrogen loss, postoperative complications, and mortality (8–10). This led to a view that high-dose opioid analgesia, which aims to obtund measured responses to surgery are key to good outcome in the high-risk surgical infant. Less is known, however, about the benefits of high-dose opioids in the context of general pediatric intensive care. Certainly, high-dose opioid administration has been shown to be beneficial in the prevention and treatment of specific situations such as a pulmonary hypertensive crisis in the at-risk infant (11) and may benefit patients with a low cardiac output state, or those with a critically balanced pulmonary to systemic shunt. Data is limited, however, outside these specific areas.

Control of stress responses can be achieved at much lower doses than those used in the earlier studies, and exposure to high-dose opioids such as fentanyl (50 μg·kg⁻¹ or higher) is associated with hypotension (12). The issue of benefits vs side effects of opioids in the critical care setting has been highlighted by the results of the ‘NEOPAIN’ study (13) in the preterm neonate. The findings have been subject to considerable debate, but suggest that in preterm neonates given morphine in a more liberal fashion than controls, observed comfort was improved at the expense of systemic hypotension. This was associated with increased risk of significant short- and long-term neurological injury and adverse outcomes. While management of the newborn is a special case, the inference in PICU is clear: provision of opioids mandates careful management to avoid hemodynamic instability whatever dose is provided. Children with severe cardiovascular compromise need careful hemodynamic monitoring and the availability of supportive therapy when first exposed to intense analgesia.

Neonates have both pharmacodynamic and pharmacokinetic susceptibility to sedatives and opioids, which may deter the clinician from providing effective dosing. However, unless effective plasma concentrations of the drug have already been achieved during surgery, initial loading doses may be required in the ICU. By contrast, in older infants and young children, it can be difficult to maintain comfort and a relatively quiescent state without large drug doses, often in combination with multiple sedative agents. This reflects increased volume of distribution, with high clearance, that may equal or exceed that of adults, and a relative pharmacodynamic drug resistance. It is not until adolescence that responses and handling of the drugs approaches that of the adult.

Pharmacokinetics of the opioids are not only age dependent but also affected by cardiac failure and cardiopulmonary bypass (CPB) surgery. Studies with morphine and remifentanil have shown that after cardiac surgery (14,15) there is a combination of an increase in volume of distribution and fall in drug
clearance. Care therefore must be taken to provide adequate drug loading early on, while individualizing continuous infusions over time to reflect reduced drug clearance, particularly in the setting of low cardiac output, and hepatic or renal impairment. Accumulation of the active metabolite of morphine, morphine-6-glucuronide, in renal failure, can lead to excessive and long-lasting sedation that delays extubation.

All opioids are associated with tolerance, resulting in increasing requirements to maintain adequate analgesia/sedation. This is accelerated by high-dose opioid techniques during anesthesia, which can cause ‘acute tolerance’, an effect which has been shown to be more pronounced in shorter acting, higher potency opioids, such as fentanyl and remifentanil (16). Neonates undergoing ECMO require five times the initial fentanyl infusion rate by day 6 to achieve an equivalent level of sedation, because of a combination of enhanced elimination (17) and pharmacodynamic tolerance (18).

Morphine is more water soluble than fentanyl, with slow onset and offset, and pronounced sedative effects, which facilitates effective analgesia following anesthesia. Loading doses of 100–200 μg·kg⁻¹·h⁻¹, followed by infusions of 10–60 μg·kg⁻¹·h⁻¹, provide reliable analgesia. Excessive sedation, respiratory depression, nausea and vomiting can be problematic. Patient-controlled analgesia, using a low background can be highly effec-

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indications</th>
<th>Dose</th>
<th>Elimination</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl Infusion</td>
<td>Analgesia</td>
<td>1–5 μg·kg⁻¹·h⁻¹</td>
<td>Hepatic metabolism</td>
<td>Large bolus doses can cause hypotension</td>
</tr>
<tr>
<td></td>
<td>Intense analgesia/ anesthetia in ventilated patients</td>
<td>10–15 μg·kg⁻¹·h⁻¹</td>
<td></td>
<td>Ventilatory depression</td>
</tr>
<tr>
<td>Bolus Fentanyl</td>
<td>Pulmonary hypertension</td>
<td>10–50 μg·kg⁻¹</td>
<td>Hepatic followed by renal excretion of active metabolite (morphine-6-glucuronide)</td>
<td>Neonates may have long elimination half-lives, with delayed recovery</td>
</tr>
<tr>
<td></td>
<td>Controlled analgesia in the extubated patient</td>
<td>Loading dose 50–200 μg·kg⁻¹, Infusion 5–80 μg·kg⁻¹·h⁻¹, Neonates: lower infusion rates 5–20 μg·kg⁻¹·h⁻¹</td>
<td></td>
<td>Delayed recovery in neonates</td>
</tr>
<tr>
<td>Morphine</td>
<td>Analgesia with sedation</td>
<td>Loading dose 50–200 μg·kg⁻¹, Infusion 5–80 μg·kg⁻¹·h⁻¹, Neonates: lower infusion rates 5–20 μg·kg⁻¹·h⁻¹</td>
<td></td>
<td>Nausea and vomiting can be problematic in older children</td>
</tr>
<tr>
<td></td>
<td>Controlled analgesia in the extubated patient</td>
<td>Loading dose 50–200 μg·kg⁻¹, Infusion 5–80 μg·kg⁻¹·h⁻¹, Neonates: lower infusion rates 5–20 μg·kg⁻¹·h⁻¹</td>
<td></td>
<td>Reduced doses may be needed with renal impairment because of accumulation of morphine-6-glucuronide</td>
</tr>
<tr>
<td>Oral morphine</td>
<td>Longer term analgesia once absorption has recovered</td>
<td>Loading dose 200–500 μg·kg⁻¹·h⁻¹, 4-hourly</td>
<td></td>
<td>Oral doses need to be larger than IV doses because of reduced bioavailability and first pass metabolism</td>
</tr>
<tr>
<td>Alfentanil Infusion</td>
<td>Rapid offset, useful for fast-track surgery</td>
<td>Loading dose: 50–100 μg·kg⁻¹, Infusion: 0.5–2 μg·kg⁻¹·min⁻¹</td>
<td>Hepatic metabolism, Highly protein bound with a small volume of distribution.</td>
<td>Small volume of distribution and short elimination half-life makes its offset very rapid</td>
</tr>
<tr>
<td>Remifentanil</td>
<td>Infusion in ventilated patients Intense, rapid onset/offset (largely independent of age or infusion duration)</td>
<td>Analgesia: 0.1–0.3 μg·kg⁻¹·min⁻¹, Anesthesia: 0.5–1.5 μg·kg⁻¹·min⁻¹</td>
<td>Metabolized rapidly by plasma and tissue cholinesterases.</td>
<td>Alternative analgesia is required before the infusion is stopped</td>
</tr>
<tr>
<td>Codeine phosphate</td>
<td>Oral medication 4-6 hourly</td>
<td>Neonate: 0.5–1 mg·kg⁻¹, Child up to 12 years: 0.5–1 mg·kg⁻¹, Adult max dose: 240 mg &gt;12 years: 30–60 mg</td>
<td>Hepatic and renal clearance</td>
<td>Also used for treatment of diarrhoea because of constipating effects</td>
</tr>
<tr>
<td>Tramadol</td>
<td>Oral medication 8 hourly</td>
<td>50–100 mg 4-6 hourly, Adult max dose: 240 mg &gt;12 years: 30–60 mg, Adult max dose: 400 mg</td>
<td>Hepatic and renal clearance</td>
<td>Only patients &gt;12 years, Nausea, vomiting, constipation Respiratory depression in large doses</td>
</tr>
</tbody>
</table>
infusion rates of 10–20
570
Pediatric Anesthesia
analgesia can be achieved with doses of 1–5
due to its relatively long elimination half-life. While
lengthy infusions (days), recovery can be prolonged
solubility and extensive peripheral uptake. After
an option for the younger child.
tive in older children, with nurse-controlled analgesia
an option for the younger child.
Fentanyl is a potent opioid, with rapid onset and
offset after short-term infusion (hours) due to its lipid
solubility and extensive peripheral uptake. After
lengthy infusions (days), recovery can be prolonged
due to its relatively long elimination half-life. While
analgesia can be achieved with doses of 1–5 μg·kg⁻¹·h⁻¹,
infusion rates of 10–20 μg·kg⁻¹·h⁻¹, may be beneficial in
infants with low cardiac output states, critically
balanced pulmonary and systemic circulations, or pul-
monary hypertension, to reduce metabolic demands
and obtund hemodynamic responses to stimuli. Five to
ten micrograms per kilograms boluses may be required
for procedures such as endotracheal suctioning and
physiotherapy. High doses may provide complete
anesthesia and sedation for neonates, while older
infants and children also require a hypnotic agent.
Alfentanil is highly protein bound, resulting in a
small volume of distribution. It undergoes rapid hepa-
tic metabolism to inactive compounds (19). Although
less potent than fentanyl, its rapid onset and offset
lend it to short-term anesthesia and analgesia.
Remifentanil is a synthetic opiate, offering potent
analgesia, with rapid, predictable offset, making it
potentially attractive for perioperative analgesia in the
pediatric cardiac patient. Its short elimination half-life,
of 3–10 min, after single injection, is relatively age
independent and not affected by renal and hepatic
function, as it is metabolized by plasma and tissue
cholinesterases (20). Peripheral accumulation does not
occur; hence, the half-life remains independent of infu-
sion duration, allowing rapid offset, which remains
predictable, despite reduction in clearance associated
with CPB (21). Effective plasma concentrations can be
rapidly achieved by continuous infusion at doses of
0.05–0.4 μg·kg⁻¹·min⁻¹, with higher doses of 1 μg·kg⁻¹
min⁻¹, required to obtund stress responses (22). It
has limited sedative effects, necessitating use with a
hypnotic.

Despite its desirable properties, its role in postopera-
tive pain management remains to be established, with
cost and drug tolerance (23), restricting its utility to
relatively short-term analgesia. Furthermore, its
potency and effects on ventilation limit its use in sponta-
neously breathing children and sick neonates, who
can develop bradycardia and hypotension on initial
exposure (22). In a study of “fast-track” pediatric car-
diac surgery, it lacked superiority over fentanyl in
terms of recovery and was associated with a significant
reduction in heart rate (24). It has potential utility for
procedural analgesia, in ventilated patients in PICU.
Given as a single intranasal dose, it provides an excel-
lent pharmacokinetic profile providing analgesia for

Table 2 Nonopioid analgesia

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indications</th>
<th>Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracetamol</td>
<td>Hyperthermia</td>
<td>0–3 months loading dose: oral 20 mg·kg⁻¹, rectal 30 mg·kg⁻¹</td>
<td>Significant but low analgesic potency</td>
</tr>
<tr>
<td></td>
<td>Co-analgesia with opioids</td>
<td>Max daily 90 mg·kg⁻¹ (max adult 4 g daily) for 48 h reduce thereafter to 60 mg·kg⁻¹</td>
<td>Reduced doses may be needed in critically ill fluid restricted child to avoid hepatic dysfunction and toxicity</td>
</tr>
<tr>
<td>Diclofenac*</td>
<td>Opioid sparing analgesia</td>
<td>Oral or rectal: 1 mg·kg⁻¹</td>
<td>Has effects on gastric mucosa and platelet function</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Max daily: 3 mg·kg⁻¹</td>
<td>Can be nephrotoxic</td>
</tr>
<tr>
<td>Ibuprofen*</td>
<td>As above</td>
<td>Oral or rectal: 10 mg·kg⁻¹ Max daily: 40 mg·kg⁻¹</td>
<td>As above</td>
</tr>
<tr>
<td>Ketamine</td>
<td>Alternative intravenous analgesia to opioids (NMDA receptor antagonist)</td>
<td>IV infusion: 10–45 μg·kg⁻¹·min⁻¹</td>
<td>Can be used in spontaneously breathing children Associated with dysphoria when used as a sole agent May provide useful bronchodilation</td>
</tr>
<tr>
<td>Clonidine</td>
<td>Less analgesic potency than morphine but can be used as co-analgesia (orally), for longer term sedation, or for withdrawal from opioids (α₂-agonist)</td>
<td>Intravenous infusion: 0.5–3.0 μg·kg⁻¹·h⁻¹</td>
<td>Can cause hypotension and bradycardia Rebound hypertension has been described in adults</td>
</tr>
</tbody>
</table>

*These drugs are used extensively outside their product licence but within recommended guidelines from the Royal College of Paediatrics and Child Health. Prevention and Control of Pain in Children 1997: BMJ Publishing Group, London. [Correction added after online publication 14 December 2010: unit of dosage for clonidine changed from μg·kg⁻¹·min⁻¹ to μg·kg⁻¹·h⁻¹]
15 min. This approach avoids fluctuant levels and the attendant side effects of single intravenous dose or infusion of remifentanil. Verghese et al. (25) have reported this technique for intubation during inhalational anesthesia with 5% sevoflurane after a single dose of 4 μg·kg⁻¹ of remifentanil. This exiting new approach would allow modulation of analgesia for procedures such as physiotherapy and endotracheal tube change, without having to modify existing infusions or break into the intravenous circuit to give additional bolus doses.

Once the alimentary route is effective, there is some evidence that oral opioid administration results in reduced longer term tolerance (26–28). Certainly, the use of enteral drug administration reduces the infection risk associated with long-term intravenous access and line manipulations (29) and should be used wherever possible. Morphine undergoes considerable first pass metabolism by the liver, if absorbed through the alimentary system, resulting in considerably greater dose requirements than by intravenous routes, with total daily doses needing to be increased by a factor of five to ten to achieve the same level of analgesia.

**Local analgesia techniques**

Afferent pain conduction can be eliminated with effective local anesthesia, with minimal side effects. Simple local anesthetic techniques can provide an important adjunct to any analgesia or sedation regimen, by reducing the background drug requirement and that for procedural analgesia. Local anesthesia can be given by a wide variety of routes that include topical, infiltration, peripheral nerve block or central continuous block (epidural or spinal). Topical anesthesia is used regularly on the general pediatric wards and in the emergency department (ED). The use of these agents in PICU is often ignored except in nonintubated patients. The pain associated with venous cannulation is sufficiently distressing, even in a moderately sedated child, to necessitate additional sedation. If agents such as Ametop and EMLA are routinely applied in advance of an anticipated procedure, the use of intravenous analgesia and sedation can be minimized. Newer, faster acting agents are now available, including lidocaine-adrenaline-tetracaine gel (LAT gel), which is effective in as little as 10 min (30,31). This agent is finding increasing favor in the ED for wound sutting, with good effect. It has been suggested that its use should be extended to other areas, such as PICU, for its rapid onset of action and excellent analgesic effects. Care does need to be given, however, to site of use, owing to the adrenaline component.

Regional anesthesia for cardiac surgery remains in the domain of a few enthusiasts rather than as a mainstream technique. A variety of retrospective publications using caudal, epidural, or spinal techniques have suggested value in the management of children after cardiac surgery, but the data remains limited and largely uncontrolled (32–34). A prospective randomized trial of spinal anesthesia with an indwelling catheter demonstrated reduced stress responses and lower blood lactate concentrations compared to a high-dose conventional opioid technique in children under 3 years undergoing major cardiac surgery (35). A similar technique to that described is currently being used by our group to provide stress reduction in the operating theater, facilitate early extubation and minimize the requirement for systemic analgesia.

**Sedation**

Sedation is a broad term when used in the context of PICU. It may facilitate several goals including (Table 3):

1. Unconsciousness (virtual anesthesia) or reduction in conscious level
2. Reduced awareness
3. Loss of explicit and implicit memory
4. Compliance with the need to lie in a confined space, attached to monitors and invasive lines
5. Prevention of distress during procedures such as physiotherapy, radiological scanning, or minor surgical intervention, which may require enhanced levels

Different drugs fulfill these roles to varying extents. Benzodiazepines, for example, provide anterograde amnesia, with reduced or complete unconsciousness at different doses, while phenothiazines and butyrophenones (chlorpromazine and haloperidol), used as major tranquilizing drugs in schizophrenia, have psychotropic properties that render the patient disinterested in activity. Some analgesic drugs reduce both pain and consciousness: ketamine provides analgesia and a dissociative anesthesia/sedation, clonidine produces analgesia and a calmed relaxed state, and morphine has additional sedative properties. Therefore, choice of a sedative regimen needs to be tailored to the individual rather than generic.

Neonates are a special group, in that morphine alone can often provide sufficient analgesia and sedation. Outside this period, however, an analgesic and a sedative drug are almost always necessary. Where neuromuscular blockade is required, a sedative drug given at an adequate dose becomes mandatory to prevent awareness.
In the past, patients in adult ICU have been given an opioid in combination with a low dose of anesthetic agent to ensure pain relief, hemodynamic stability, and tolerance to the constraints of ITU. The potentially lethal side effects of anesthetic drugs used over days have only emerged after reviews of death rates and analysis of recurring adverse events. These have included immunomodulation by barbiturates (36,37), adrenocortical suppression by etomidate (38) and more recently, mitochondrial dysfunction with propofol, in both adults and children (39).

As with opioids, delivery via the enteral route may avoid complications associated with intravenous delivery, provided enteric function is intact. Many of the sedative agents are well absorbed and tolerated enterally, including benzodiazepines, clonidine, and chloral hydrate. An additional advantage to oral sedation is that it can be weaned gradually and continued following discharge from ICU, if necessary.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Benefits</th>
<th>Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepines</td>
<td>Amnesic benefit in addition to sedation</td>
<td>Intravenous infusion: max 200 µg·kg⁻¹·h⁻¹</td>
<td>High risk of withdrawal with prolonged use or high doses (&gt;100 µg·kg⁻¹·h⁻¹). Helps control seizures</td>
</tr>
<tr>
<td>Midazolam</td>
<td></td>
<td>Intranasal: 0.1 mg·kg⁻¹ each nostril</td>
<td></td>
</tr>
<tr>
<td>Lorazepam</td>
<td>Oral drug useful in midazolam withdrawal</td>
<td>Rectal: Neonate: max 2.5 mg 1 month–3 years: 5 mg 3–12 years: 5–10 mg 12–18 years: 10 mg</td>
<td>Risk of respiratory depression – particularly with repeated doses</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Status epilepticus (rectal)</td>
<td>Intravenous infusion: max 4 mg·kg⁻¹·h⁻¹ Titrated to effect</td>
<td>Hypotension</td>
</tr>
<tr>
<td>Propofol</td>
<td>Short-term action – rapid wake up</td>
<td>Intravenous infusion: Check for rising lactate or acidosis, limit infusion duration</td>
<td>Risk of propofol infusion syndrome. Lipid load with infusion. Contraindicated by FDA</td>
</tr>
<tr>
<td>Volatile agents</td>
<td>Rapid clearance for quick wake up</td>
<td>Dose titrated to effect Depends on delivery system and gas flows</td>
<td>Can be useful for bronchospasm and seizures Requires vaporizer and scavenger systems</td>
</tr>
<tr>
<td>Chloral hydrate</td>
<td>Well tolerated</td>
<td>Oral or rectal: 25–50 mg·kg⁻¹</td>
<td>Delayed clearance in neonates – be wary with regular dosing</td>
</tr>
</tbody>
</table>

[Correction added after online publication 14 December 2010: unit of dosage for clonidine changed from µg·kg·min⁻¹ to µg·kg·h⁻¹]

Early extubation

Early extubation, with good analgesia that allows rapid mobilisation and recovery, is likely to be beneficial in terms of reducing postoperative complications, although the results of more general outcome studies remain inconclusive (2,40). It should be added that a precondition of early extubation is that the postoperative repair and cardiovascular function are adequate to support an awake, mobilizing infant. Accelerated convalescence confers benefits in both medical and economic terms, in that earlier discharge from the ICU improves throughput. The last 10 years has seen a widespread acceptance of fast-track pediatric surgery, with rapid extubation not only for simple cases but also for more complex procedures (41,42). There may be specific advantages in immediate extubation for some cardiac conditions. For example, those with single ventricle physiology (following Glenn shunt/Fontan
repair), and Fallot's Tetralogy, when reduced in-"trathoracic pressure, associated with spontaneous breathing, improve pulmonary blood flow and oxygenation (43).

A variety of techniques have been described, including the use of regional analgesia; however, the difficulties lie not with on table extubation but with managing pain and sedation in ICU. Children need to remain sufficiently sedated after surgery to prevent restlessness with attempts to remove vital monitoring or invasive catheters. In the authors' experience, this usually necessitates a combination of both analgesia (opioids, acetaminophen, and NSAIDs) and sedation (a benzodiazepine or alpha-2 agonist). Excessive use of potent opioids during surgery promotes acute tolerance, leading to a requirement for increased analgesia after surgery (16). The debate on whether 'pharmacological restraint' is always preferable to limited physical restraint, such as bandages around the hands, arm splints or even true restraint, remains unresolved and provokes strong views.

Continuing anesthesia for a short time after surgery in PICU allows time to assess the surgical repair and ensure that the patient has been optimized prior to extubation. Several techniques have been described, including infusions of propofol (5) and remifentanil with midazolam (15) that allow a controlled emergence. The use of propofol in PICU remains contentious because of the issues surrounding 'Propofol Infusion Syndrome' (39,44). Despite these concerns, and its contraindications for use by regulatory authorities in the USA and UK, it continues to be used short-term, at low dose (<4 mg·kg⁻¹·h⁻¹) for specific cases. Patients on a propofol infusion should be closely monitored for rising lactate, acidosis, reduced urine output or dysrhythmias.

Remifentanil combined with low-dose midazolam provides very reliable analgesia and sedation for early extubation. Recent studies have shown that there is a good correlation with drug infusion rate, plasma level, and COMFORT score (15). Before withdrawal of remifentanil, a loading dose of opioid is needed to remove. Examples include those with cardiac failure, pulmonary hypertension, lung or airway disease, or ongoing sepsis. These patients are the most at risk from drug tolerance and subsequent withdrawal. Some agents are considered more problematic than others: the incidence of withdrawal with midazolam has been reported as frequently as 35%. Limiting midazolam infusion to 100 μg·kg⁻¹·h⁻¹ reduces the likelihood of withdrawal, but stopping the drug slowly does not reduce the risk (45).

Techniques that can be used in PICU to limit the problems associated with long-term sedation include:

1. Drug cycling: changing pharmacological drug groups routinely to reduce the emergence of tolerance
2. Sedation holidays: temporary cessation of sedative drugs to evaluate emergence.
3. Nonpharmacological techniques: oral sucrose, reducing environmental stress (noise, light, interruption of day–night cycle), swaddling, etc.
4. Transfer to oral sedation where possible.

In adult intensive care, percutaneous tracheostomy is often performed at an early stage. This allows the patient to be ventilated while awake with minimal sedation, allowing the patient to breath with support ventilator modes, cough and clear their own secretions more effectively, reducing the risks of nosocomial chest infections. Unfortunately, this technique cannot be applied in children because of the technical issues associated with smaller airways and the continuing need for sedation. Surgical tracheostomy and insertion of a long-term indwelling central venous catheter can, however, allow the patient who requires longer term ventilator support to be managed with little or no sedation.

Neuromuscular blockade can be useful in patients that are difficult to ventilate, such as for inverse ventilatory ratios, high-frequency oscillation, or to deliberately hyper or hypoventilate them depending on their underlying pathology (46). It continues to be used in children that require hypothermia owing to dysrhythmia or to reduce metabolic rate and oxygen demand. Neuromuscular blockade is used more commonly than in adult ICU, but as a specialty we are now using it less frequently (47), with recent reports estimating the use of long-term neuromuscular blockade in 14–16% of ventilated days in PICU (48). Avoidance of prolonged use is preferable because of the risks of critical care polyneuropathy (49) and drug accumulation, which may result in delayed extubation.

Withdrawal phenomena remain a major concern in those patients who received sedation over many days. Symptoms can include sweating, tachycardia, hypertension, agitation, posturing, withdrawal, vomiting, and
diarrhea. Occasionally, this prompts concerns of, and investigation for, cardiac, neurological, or gastrointestinal disease. The alpha-2 agonist clonidine, chlorpromazine, and haloperidol can be used effectively to moderate these effects, and the patients discharged to wards on a weaning oral regimen over a period of 7–14 days. Concerns remain about abrupt cessation of clonidine and the risk of rebound hypertension.

Assessment of pain and sedation

Sedation is administered to critically ill children according to predicted requirement. This may not, however, reflect actual requirements, with significant individual variation. Assessment of depth of sedation, with titration of analgesic and sedative drugs, is important to ensure comfort and avoid adverse outcomes, associated with under or over-sedation.

Several scales, assessing behavioral and/or physiological measures have been developed and validated for this purpose. These include ‘The COMFORT Scale’, an objective measure of distress in ventilated pediatric patients, validated in all age groups (50,51). It comprises eight variables, each rated 1–5: alertness, calmness/agitation, respiratory response, physical movement, heart rate, blood pressure, muscle tone, and facial tension, the scale ranging from 0 to 40, with a target range of 17–26. As with other scoring systems, it is limited by inter-observer variability, provides only intermittent data and cannot be used in the context of neuromuscular (NMJ) blockade. Cardiovascular responses are also difficult to assess in patients who are paced.

Neurophysiological methods and auditory evoked potentials have been evaluated in the research domain. Bispectral Index (BIS) monitoring utilizes data from electroencephalogram (EEG) to measure depth of anesthesia. This technique assumes changes in frequency are related and looks for phase coupling among frequency bands (biocoherence) (52,53). In awake individuals, there is minimal synchronization because of multiple signal generators within the brain, whereas during sleep, there is less activity and the EEG reflects coupling between signal generators (52,53). A dimensionless value, ‘the BIS number’, is calculated, which ranges from 0 to 100, 0 indicating an isoelectric state, with 100 correlating with a fully awake individual. Values of 40–60 are seen with general anesthesia (54). While it may provide an accurate assessment of depth of sedation for single agents such as midazolam, propofol, and volatile agents, this is not the case for opiates or ketamine (55,56). Furthermore, Messner et al. (57) demonstrated BIS Index to decline, with NMJ blockade in awake volunteers, suggesting it may not identify those inadequately sedated under muscle relaxant. The BIS monitor is age dependent (58), and currently there is insufficient evidence to support routine use of the BIS monitor, or any other neurophysiological sedation scoring technique, in PICU (59).

Future prospects

The concept of using the volatile agents for longer-term sedation on ICU’s is not a new one. Barriers in the past have been ways to safely deliver the drug (vaporizers) as well as protecting the staff and environment (scavenging systems). A few ICU ventilators in the past such as the servo 900c were able to provide a plug on vaporizer to deliver isoflurane to the critically ill patient, but these are now generally obsolete. Adult data has shown that isoflurane can be an effective and practical sedative drug in the ICU when combined with opioids with few side effects (60,61). More recently, Meiser et al. (62) have shown the rapidly eliminated inhalational agent desflurane to have characteristics that make it superior to other more conventional agents. The data in PICU is very limited. The early 10 patient study by Arnold et al. (63) used relatively high doses of isoflurane as a single agent in patients who had already become tolerant to opioids. Their results showed that while the drug was effective, there was a high incidence (50%) of tolerance agitation and dystonia on withdrawal of the drug. More recent reports, particularly for treatment of status asthmaticus, as part of a more balanced sedative regimen, have been more encouraging (64,65). However, there is major lack of good prospective data to evaluate the potential of these drugs in PICU.

The renewed interest in gaseous sedative agents is likely to continue with developments of new delivery systems within ICU. Early studies with xenon show great potential in the clinical areas of the developing neonate and neurological injury (66,67). Unlike many PICU sedative agents, including midazolam, ketamine, and other volatile anesthetic agents, xenon has been shown in animal models to provide anesthesia and sedation without producing apoptosis (68). Further studies have found that xenon can offer protection from hypoxic injury. Hobbs et al. (69) demonstrated that rat pups exposed to hypoxic injury had a significantly better outcome with the combination of cooling to 32°C and xenon. The functional improvement with this regimen was almost complete, sustained long-term, and accompanied by greatly improved histopathology. Chakkrapani and colleagues demonstrated similar neu-
Protective benefits of xenon, with synergistic effects seen with hypothermia in asphyxiated newborn piglets (70). Issues still remain whether this drug is to become viable in PICU. It is rare, expensive and requires a closed system of delivery, which necessitates the development of new ventilatory systems.

References

Analgesia and sedation after pediatric cardiac surgery

A.R. Wolf and L. Jackman


REVIEW ARTICLE

Pediatric heart transplantation: demographics, outcomes, and anesthetic implications*

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Keywords
pediatric cardiac transplantation; pediatric anesthesia; transplant outcomes; cardiomyopathies; congenital heart disease; failed Fontan

Summary
The evolving demographics, outcomes, and anesthetic management of pediatric heart transplant recipients are reviewed. As survival continues to improve, an increasing number of these patients will present to our operating rooms and sedation suites. It is therefore important that all anesthesiologists, not only those specialized in cardiac anesthesia, have a basic understanding of the physiologic changes in the transplanted heart and the anesthetic implications thereof.

Introduction
The first ‘successful’ pediatric heart transplant was in 1967 in an 18-day-old baby with tricuspid atresia who survived 6 h (1). It was not until the late seventies that survival became realistic with the introduction of cyclosporine, advances in donor management, organ preservation, and recipient selection, development of the transvenous cardiac bioprobe for rejection surveillance, and clarification of brain death criteria. In 1982, the International Society of Heart and Lung Transplantation (ISHLT) opened a voluntary registry for pediatric heart transplantations (<18 years); since then, >8000 children have been registered and followed. Children account for ~12.5% of cardiac transplantations, with ~450 pediatric transplants reported yearly from 80 centers (most in Europe and North America) (Figure 1) (2). This article reviews current trends and outcomes for pediatric cardiac transplantation and discusses important anesthetic implications.

Indications and demographics
The major indications for heart transplantations in infants and children are cardiomyopathy, congenital heart disease (CHD), and re-transplantation (3,4).
Cardiomyopathies (CM)

CM fall into three types: dilated, hypertrophic, and restrictive, each with different risk factors, clinical courses, outcomes, and treatment options.

Dilated cardiomyopathy (DCM). DCM is the most common pediatric cardiomyopathy (>50%), accounting for 75% of transplantations for CM. It is caused by neuromuscular disorders, viral myocarditis, chemotherapeutic agents, metabolic diseases, and genetic factors (5). Treatment includes β-blockers, vasodilators, diuretics, and biventricular pacing, with most studies showing a 5-year survival rate of 40–80% (6,7); the subgroup of viral myocarditis has the best chance of recovery within the first 2 years (freedom from death or transplantation of 70% at 1 year and 50% at 5 years after the diagnosis) (8,9).

Hypertrophic cardiomyopathy (HCM). HCM constitutes about 25% of pediatric CM and is characterized by ventricular hypertrophy not caused by an underlying obstruction or stenosis. Seventy-five percent of cases are idiopathic, with inborn errors of metabolism (Pompe disease), malformation syndromes (Noonan, Beckwith-Wiedemann), and neuromuscular disorders (Friedreich’s ataxia) also being associated with HCM (10,11). Children with inborn errors of metabolism and those with early presentation in infancy, lower shortening fraction, and higher posterior wall thickness on echocardiography are at high risk of death. Progression to a dilated or restrictive cardiomyopathy is often the indication for transplantation (12).

Restrictive cardiomyopathy (RCM). Restrictive cardiomyopathy (RCM), a diastolic cardiac dysfunction defined as restrictive filling with normal ventricular size and wall thickness, is rare in children (2.5–3%) (10,13). It responds poorly to medical or surgical treatment and can lead to significant pulmonary hypertension. Survival rates for 1, 5, and 10 years after diagnosis are 80%, 39%, and 20%, respectively, thus transplantation is considered early in the disease process (14–16).

CHD

Initially, a primary indication for management of hypoplastic left heart syndrome (17), transplantation was limited by the low number of available organs for infants and high waiting list mortality. Advances in cardiac surgery and pediatric cardiology for complex CHD have significantly improved survival, resulting in a shift away from heart transplantation in infants as a primary therapeutic modality (Figure 2). Current indications are previously repaired or palliated CHD with poor ventricular function, with single ventricle lesions (especially the failing Fontan) accounting for the majority (36%) of CHD patients transplanted (17–19).

Re-transplantation

Retransplantation is a small, but steadily growing percentage of heart transplantation (6–7%). The major indications are posttransplant coronary vasculopathy (51%) and graft failure (16%) (2). Unfortunately, survival after re-transplantation is inferior to that seen after primary transplantation (20).

The pattern of indications for pediatric heart transplantation has changed over the past 23 years. From 1988 to 1995, 78% of transplants occurred in infants for CHD (mostly hypoplastic left heart syndrome) and 16% for CM (21). More recently (1996–2008), 63% of transplantations in infants occurred for CHD and 31% for CM. In older children, cardiomyopathy is the major indication (64%), with CHD accounting for 24% and re-transplantation 7% (21). North America has the highest proportion of infant heart transplantations (27%) compared to the rest of the world (11%) (2).

Figure 1 Age distribution of pediatric heart recipients (by year of transplant) (2, 21).
Contraindications
In addition to general contraindications (active malignancy, uncontrolled infection, multi-organ failure, psychosocial factors), irreversible pulmonary hypertension (>6 Wood Units·m⁻²) or severe organ dysfunction (cirrhosis, renal insufficiency, major neurodevelopmental disorder or stroke) can be exclusion criteria (3,4). Current controversies include indications for combined organ transplants (heart–kidney/liver/lung), controlled infections (HIV, hepatitis), or malignancies (22–24).

Timing of transplantation and waiting list mortality
Generally, transplantation is considered when it offers an important survival advantage over alternative management options. According to the American Heart Association, heart transplantation is a Class 1 (Level B) recommendation for children with stage D heart failure and Class 1 (Level C) for stage C heart failure (3,25) (Table 1). The United Network for Organ Sharing (UNOS) will list these children as Status 1A or 1B in their medical urgency allocation algorithm (26) (Table 2).

As of June 11, 2010, there were 3142 patients on the US waiting list for heart transplantation, including 262 infants and children. The median waiting time for children is about 80 days, compared to 170 days for adults <65 years of age (27). Unfortunately, children have the highest waiting list mortality. An analysis of 3098 children listed for transplant in the United States between 1999 and 2006 found that 17% died while waiting, 63% were transplanted, 8% recovered, and 12% remained listed (28). Most of the children who died on the waiting list weighed <15 kg. Multivariate predictors of waiting list mortality (hazard ratio 1.9–3.1) included extracorporeal membrane oxygenation (ECMO), CHD, ventilator support, dialysis, listing status 1A, and nonwhite race/ethnicity. The level of invasive hemodynamic support was a stronger predictor of mortality at 30 days than UNOS status. For example, an infant (<10 kg) on ECMO for CHD had a 12-fold increased risk of death compared to a child >10 kg with cardiomyopathy on inotropic support, although both would be listed as UNOS 1A. This study highlighted a major problem of the current organ allocation system, namely the increasing conflict between medical urgency and waiting list seniority.

Outcomes
Survival
The average survival (time at which 50% of recipients remain alive) varies with the age of the recipient at transplant. The average survival is 18 years for infants, 15 years for children aged 1–10 years, and 11 years for teenagers (Figure 3) (2). The highest risk of dying is within the first 6 months and is mainly caused by acute rejection or infection. Risk factors for 1-year mortality include the degree of pretransplant support (ECMO, ventilator, dialysis), a diagnosis of CHD, re-transplantation, severe infections, panel reactive antibodies ≥10%, increased donor age, and earlier era of transplant. Inotropic support, hos-

<table>
<thead>
<tr>
<th>Stage</th>
<th>Interpretation</th>
<th>Clinical Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>At risk of developing heart failure</td>
<td>Congenital heart defects, Family history of cardiomyopathy, Anthracycline exposure</td>
</tr>
<tr>
<td>B</td>
<td>Abnormal cardiac structure/function</td>
<td>Univentricular hearts, Asymptomatic cardiomyopathy</td>
</tr>
<tr>
<td></td>
<td>No symptoms of heart failure</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>Abnormal cardiac structure/function</td>
<td>Repaired or unrepaired congenital heart disease, Cardiomyopathies</td>
</tr>
<tr>
<td></td>
<td>Past or present symptoms of heart failure</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>Abnormal cardiac structure/function</td>
<td>Continuous i.v. infusion of inotropes or PGE₁, Mechanical ventilatory and/or circulatory support</td>
</tr>
</tbody>
</table>

Figure 2 Diagnosis in pediatric heart recipients (age <1 year) (2, 21).

Table 1 Heart failure staging in children, Modified from (25)
hospitalization, previous malignancy, ischemia time, cytomegalovirus, or HLA mismatch had no effect on 1-year mortality. Survival rates have improved in the recent era, primarily because of increased survival during the first 6 months. Preliminary data suggest a 30% improvement in the risk-adjusted 5-year survival rate. On the other hand, media and long-term outcomes have not been significantly affected by advances in posttransplant care. Centers with higher pediatric transplant volume generally have better survival rates (2).

Causes of death

Nearly 50% of deaths within 30 days are caused by graft failure (primary or secondary to rejection) and technical factors. Acute rejection, infection, and multiple organ failure each account for about 10%. During the first 3 years, acute rejection is the leading cause of death, whereas after this period almost 60% of deaths are attributable to coronary allograft vasculopathy (CAV) or graft failure (2).

Transplant morbidity

With improving survival, the focus of posttransplant care is shifting toward transplant morbidity (2).

Functional status. There are only limited data available for children who have survived at least 10 years after transplantation; 92% are reported to have no limitations on physical activity, and 1% requires total assistance. Growth rate is normal in the majority of transplant recipients. Up to a quarter of patients may have difficulties with emotional adjustment.

Rehospitalization. Within the first year, 50% of children need to be hospitalized: 35% for infection, 25% for rejection, and 15% for both. By 10 years, this number drops to about 25% (infections [36%], rejection [15%], or both [4%]) and is similar to adult data (2).

Rejection. Rejection is one of the major complications and remains an ever present threat. Approximately 30–
35% of children experience at least one episode of acute rejection within the first year, despite the increasing use of induction agents. The incidence begins to decline after 3 years, reaching about 12% between 5 and 10 years. Of note, adolescents are notorious for low compliance (up to 20%) with antirejection regimens. Rejection is not only one of the major causes of death, but it is also associated with the development of cardiac allograft vasculopathy and therefore graft survival (29,30).

Recipient CD4 T cells recognize foreign antigen in the donor heart, triggering T-cell activation, interleukin-2 (IL-2) secretion, and activation of monocytes/macrophages, B cells, and cytotoxic CD8 cells. Prevention and ongoing suppression of such activation is the fundamental concept behind immunosuppressive therapy. The majority of centers use an induction phase followed by a maintenance regimen.

The induction phase is purported to reduce the incidence of early rejection and possibly delay or avoid treatment with nephrotoxic agents. This is generally achieved by the depletion of the T-cell pool with monoclonal or polyclonal antibodies or prevention of IL-2 secretion with specific IL-2 receptor antagonists. Compared with classical agents like cyclosporine, renal dysfunction is less likely with these agents. Induction agents include the following: (i) OKT3 is a murine monoclonal antibody directed against CD3 molecules on T cells; (ii) Rabbit or equine antithymocyte globulin (ATG) are polyclonal IgG antibodies extracted from thymocytes; (iii) Basiliximab and daclizumab, in contrast to OKT3 and ATG, are specific IL-2 receptor antibodies that are usually well tolerated and increasingly being used; currently, 22% of pediatric heart transplant recipients are treated with these specific IL-2 receptor antibodies. The most recent ISHLT registry reports that 60% of pediatric cardiac recipients received an induction therapy in 2008, a significant increase from 37% in 2001. Nevertheless, the incidence of rejection episodes between discharge and 1 year has not decreased, nor has the choice of induction agents influenced survival (2).

Several classes of drugs are currently used for maintenance immunosuppression, including corticosteroids, calcineurin inhibitors (cyclosporine, tacrolimus/FK506), antiproliferative agents (azathioprine, mycophenolate mofetil [MMF]), and target of rapamycin inhibitors (sirolimus) (31). Corticosteroids are nonspecific antiinflammatory agents, but because of their deleterious side effects, especially on growth and glucose metabolism, most transplant centers try to restrict or avoid their use for routine immunosuppression. Cyclosporine and tacrolimus (FK506) inhibit the transcription of the IL-2 gene, thereby reducing the production of IL-2. Cyclosporine therapy is often complicated by hypertension, nephrotoxicity, neurotoxicity, liver dysfunction, hyperlipidemia, hypertrichosis, gingival hyperplasia, and posttransplant lymphoproliferative disease (PTLD). Tacrolimus (FK506) has a slightly different side-effect profile than cyclosporine (higher incidence of diabetes and neurotoxicity with similar nephrotoxicity) and might be more effective. Consequently, it is increasingly replacing cyclosporine in many protocols (32–34). Antiproliferative agents inhibit B- and T-cell proliferation; MMF is replacing azathioprine in many centers because of less bone marrow suppression and nephrotoxicity. Sirolimus, because of its adverse effects on wound healing, bone marrow function, and triglyceride levels, has mainly been used for rejection therapy. This might change in the future because adult studies suggest that sirolimus may reduce the progression of coronary vasculopathy (35).

Many pediatric centers use a combination of triple immunosuppression therapy for maintenance for the first year: 38% received cyclosporine, 58% tacrolimus, 20% azathioprine, 59% MMF, 55% prednisone, and 8% sirolimus. Between years 1 and 5 after transplant, there is a trend toward reducing the number of agents, early steroid withdrawal, and reduced use of cyclosporine and azothioprine in favor of tacrolimus and MMF (2).

Rejection surveillance. Despite induction therapy, the first-year rejection rate (30–35%) has not decreased (2). The diagnosis of rejection is made on clinical signs, echocardiographic evidence of ventricular dysfunction, and endomyocardial biopsy (36). Rejection episodes can be classified into acute vs chronic, cellular vs antibody mediated, and with or without hemodynamic compromise (31). Rejection with hemodynamic compromise seems to occur twice as often in children: 11% compared to 5% in adults (37,38). Treatment strategies for rejection episodes are based upon the etiology and severity, and usually include a 3-day pulse with steroids or ATG, and if antibody-mediated rejection, the addition of i.v. immunoglobulin, plasmapheresis, or both. Bortizemab, a proteasome inhibitor directly targeting the antibody-producing plasma cells, is the newest addition to the antirejection armamentarium and currently undergoing investigation (39–42). For children, rejection surveillance with serial endomyocardial biopsies is complicated by patient size, difficult vascular access, and the need for anesthesia or deep sedation. The timing of biopsies is tailored to the probability of rejection; the first is usually obtained 7–14 days after transplant, and further biopsies are performed at 4-, 6-, 9-, and 12-week posttransplant, then
at 6 and 9 months. After the first year, most centers continue surveillance with 6 monthly biopsies and annual coronary angiography. In the near future, gene expression profiling of peripheral blood specimens will reduce the need for frequent endomyocardial biopsies (43,44).

**Cardiac allograft vasculopathy.** At 10 years, 34% of children have CAV (2), with the onset of CAV influenced by age at transplantation. Freedom from CAV 8-year posttransplant is higher in infants and younger children (71% and 74%, respectively) than in children >11 years (56%). Once CAV occurs, the 3-year graft survival is 45% for all pediatric age groups. As adults have a 50% graft loss at 9 years after CAV diagnosis, it is uncertain whether CAV causes a more aggressive rate of graft deterioration in younger patients or whether CAV is diagnosed earlier in adults as a result of more aggressive surveillance (45). It is also unclear why short ischemic times (<2 h) increase the incidence of CAV in children younger but not older than 10 years.

**Renal dysfunction.** Ten years after transplant, 11% of children and adolescents compared with 60% of adults have severe renal dysfunction (dialysis, kidney transplant, serum creatinine >2.5 mg/dl). 1)

**Malignancy.** Eight percent of children develop malignancies at 10 years after transplant in contrast to 32% of adults. Almost all pediatric malignancies are lymphomas in contrast to the skin or nonlymphoma tumors seen in adults.

**Hypertension.** Eight years after transplantation, 69% of pediatric survivors had hypertension, compared to 94% of adults at 5 years.

**New developments**

ABO-incompatible transplantation in infants, donation after cardiac death, and the increasing number of single ventricle patients with a failed Fontan palliation represent some of the latest developments in pediatric cardiac transplantation.

**ABO-incompatible heart transplantation in infants**

A shortage of donor organs, especially for infants, and the high waiting list mortality have triggered the search for new concepts to enlarge the available donor pool (46). In the adult population, ABO-incompatible solid organ transplantations are absolutely contraindicated because of hyperacute rejection mediated by preformed antibodies. However, the immature immune system of newborns does not produce isohemagglutinins and levels remain low until 12–14 months of age; in addition, the complement system is not fully competent in young infants. As a result, infants can be recipients of ABO-mismatched organs. This concept has been successfully used over the last decade, and the existing data suggest that outcomes are similar to matched recipients as long as important criteria and strategies are followed: the ABO-mismatched organ recipient must be <15 months of age, have low or no isohemagglutinins levels, and fulfill all other transplant criteria (46,47). During the pretransplant phase, recipients typically receive a two times blood volume exchange transfusion, which can be repeated several times depending on the level of isohemagglutinins checked periodically during surgery and in the postoperative period. The removed blood cells can be ‘washed’ in a cell saver and retransfused.

**Donation after cardiac death**

The concept of donation after cardiac death or transplantation after declaration of cardiocirculatory death (DCD) was reintroduced in the late nineties. With the consent of the family, nonbrain-dead children with a terminal diagnosis (e.g. severe cerebral hemorrhage) are taken to the operating room, prepared for organ retrieval, and support is withdrawn by the primary care or critical care physician. Death is declared after cardiopulmonary arrest, and there is an additional waiting period of several minutes before organs are harvested. Concerns about myocardial hypoxic-ischemic injury during the prearrest time initially discouraged the harvesting of hearts, but evidence suggests a ‘safe’ hypoxic-ischemic time of up to 30 min (48). Despite ongoing ethical and medical controversies, the first experiences with DCD in the pediatric population have been encouraging (49). One report compared outcomes of three DCD infant cardiac transplantations with 17 infants with conventional donation after brain death (50). The 6-month survival rate was 100% in the DCD group and 84% in the conventional group; there was no difference in the number of rejection episodes or echocardiographic indicators of ventricular dysfunction.

**Failed Fontan**

Children with single ventricle hearts and failed Fontan palliation represent the largest and fastest growing
group of transplant candidates with CHD (51). Indications include severe ventricular dysfunction, atrioventricular valve regurgitation, pulmonary hypertension, or long-term complications of Fontan physiology such as protein-losing enteropathy, plastic bronchitis, intractable arrhythmias, thromboembolism, hepatic and renal dysfunction, ascites, and pleural effusions. These children (and adults) have had numerous hospitalizations and are often in poor physical and mental condition; they are ‘high-risk’ transplant candidates and require thorough preoperative evaluation. The risk of bleeding is markedly increased because of underlying coagulopathies, multiple previous surgeries, the presence of aortopulmonary collaterals, and the need for pulmonary artery reconstruction. Malnourishment and electrolyte imbalances can aggravate preexisting arrhythmias and predispose to poor wound healing and infection. Adequate nutritional support and advanced imaging studies, including cardiac catheterization with liver biopsy and coil occlusion of collaterals, are important aspects of pretransplant management (52). A retrospective multi-institutional review of pediatric Fontan patients listed for cardiac transplantation between 1993 and 2001 reported the survival rate on the waiting list as 78% at 6 months and 74% at 12 months, which is comparable to other transplant candidates (19). Eighty percent of deaths on the waiting list occurred within the first 6 months of listing, with risk factors being ventilatory support, UNOS status 1, age < 4 years, and shorter interval since the Fontan procedure (<6 months). The actual survival rates after transplantation were 77% at 1 year, slightly less but not significantly different from data for other recipients [Non-CHD (91%) or other CHD indications (85%)]. Interestingly, protein-losing enteropathy resolved in all children who survived 30 days. There are also reports from individual institutions (53).

**Physiology of the transplanted heart**

After transplantation, the function of the surgically denervated heart is dependent on an intact Frank Starling mechanism (ability of the myocardium to increase contractility and hence stroke volume in response to stretch [preload]) and stimulation from endogenous circulating catecholamines. The transplanted heart is characterized by elevated filling pressures, increased end-diastolic and end-systolic volumes, low normal left ventricular ejection fraction, and a restrictive physiology (diastolic dysfunction). The left ventricular end-diastolic pressure is typically around 12 mmHg 4–8 weeks after transplantation. Afferent and efferent denervation have multiple effects on circulatory control mechanisms, including altered cardiovascular responses to exercise, cardiac electrophysiology, and responses to cardiac pharmacologic agents (Table 3) (54). Exercise testing demonstrates that transplanted children can usually achieve only 60–70% of normal capacity. Exercise generates an increase in cardiac output by increases in stroke volume, a highly preload-dependent process, with tachycardia occurring only later in response to circulating catecholamines; the peak heart rate achieved is lower than normal. There are several case reports of profound bradycardia and even cardiac arrest after administration of neostigmine for reversal of neuromuscular blockade (55–59). The denervated heart is extremely sensitive to adenosine, with the magnitude and duration of effect on the AV node being three to five times greater; the dose should be reduced by 50%. The lack of reflex tachycardia can lead to profound hypotension with direct vasodilators (nitroglycerine, nitroprusside, hydralazine). The incidence, timing, and extent of sympathetic reinnervation are still being investigated, but positive effects on cardiac performance during exercise have been demonstrated (60).

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Physiology of the transplanted heart. Modified from (54)</th>
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<tbody>
<tr>
<td>Elevated filling pressures</td>
<td>Low normal left ventricular ejection fraction</td>
</tr>
<tr>
<td>Restrictive physiology (stiff heart)</td>
<td>Increased afterload (hypertension)</td>
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<tr>
<td>Afferent denervation</td>
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</table>
  - Silent ischemia  
  - Altered cardiac baro-and mechanoreceptors  
  - Less stress-induced increase in systemic vascular resistance  
  - Increased blood volume (decreased natriuresis and diuresis) |
| Efferent denervation | 
  - Resting tachycardia (loss of vagal tone)  
  - Impaired chronotropic response to stress (dependent on circulating catecholamines) |
| Electrophysiology | 
  - Sinus node dysfunction in immediate postoperative period  
  - Normal AV node conduction  
  - Shift from β1 to β2 receptors  
  - Altered response to medications |
| No heart rate response to atropine or glycopyrrolate | Decreased response to digitals; possible severe bradycardia |
| Cardiac arrest with neostigmine | Exacerbated response to Ca++channel blockers, β-blockers, adenosine |
| Exacerbated response to direct acting sympathomimetic agents | Decreased response to indirect acting agents (dopamine, ephedrine) |
| Possible sympathetic reinnervation | Enhanced contractile response and exercise tolerance |
| Higher peak heart rates during exercise |
Anesthetic considerations for the transplanted heart

Anesthesia for patients with a transplanted heart is reviewed in detail elsewhere (61–63). The preoperative evaluation should specifically focus on cardiac function, current rejection status, presence of infections, evidence of cardiac allograft vasculopathy, status of vascular access, organ dysfunction, side effects of steroids and other immunosuppressive agents (frequently hypertension, renal dysfunction, bone marrow suppression), and psychological status. A thorough review of recent surveillance testing (echocardiography, ECG, endomyocardial biopsies, cardiac catheterizations, and coronary angiography) is essential. Any decrease in exercise tolerance or new onset of dysrhythmias should raise a high index of suspicion for rejection and/or CAV. Consultation with the patient’s cardiologist as to their current status can be extremely beneficial and is therefore strongly recommended.

The anesthetic plan depends on the patient’s physical status and the nature of the procedure. The importance of adequate preload, slower adaptive responses (denervation and dependency on circulating catecholamines), reduced inotropic and chronotropic reserve, and altered responses to cardiac pharmacologic agents is discussed earlier. Use of hemodynamic responses to noxious stimuli to assess adequacy of depth of anesthesia is limited.

Many anesthesia techniques have been successfully used for children with transplanted hearts. Adequate hydration and appropriate drug selection are important to avoid hypotension. Hypotension is best managed with a fluid bolus and a direct-acting sympathomimetic, if necessary, while maintaining an adequate depth of anesthesia. The increased risk of infection requires strict attention to aseptic techniques and appropriate antibiotic coverage. For the same reasons, the oral route is preferred to the nasal for endotracheal intubation. A careful risk/benefit analysis must precede the use of invasive monitoring. When planning central venous access and pressure monitoring, it should be remembered that endomyocardial biopsies are typically performed via the femoral vessels in infants and young children, and via the right internal jugular vein in older children and adults. Consideration should be given to preserving these sites for later use, if possible.

Maintenance of adequate immunosuppression in the perioperative period is essential. Postoperative gastric dysfunction can delay or impair the absorption of cyclosporine and tacrolimus, and many medications used in the perioperative period can affect immunosuppressive drug levels. Close monitoring and frequent dose adjustments are often required and should be carried out in consultation with the transplant cardiology team.

Anesthesia for pediatric cardiac transplantation

Anesthesia can be quite challenging, depending on the indication for transplant and the age and clinical status of the child. Children with CM can present in critical condition on inotropic support and pulmonary vasodilators (milrinone, dobutamine) or with a ventricular assist device being used as a bridge to transplant. Children with previously repaired or palliated CHD are frequently underweight, malnourished, and anemic from longstanding low cardiac output, feeding problems, or protein-losing enteropathy (failing Fontan) (51–53). They are often very scared and in our experience very tolerant to sedatives and analgesics. Vascular access (arterial and/or venous) can be limited as the radial arteries may be occluded from previous use and the femoral arteries and veins from previous cardiac catheterizations and surgical access. A thorough preoperative assessment and discussion with the surgical team to specify potential alternative sites for central venous and arterial monitoring as well as peripheral bypass cannulation are essential to avoid surprises and confusion in the operating room. The potential for massive bleeding is significant as a result of scarring and adhesions from multiple previous surgeries, collateral vessels, and preexisting coagulopathy; this can prolong the dissection phase. Close coordination with the donor retrieval team is important to minimize the ischemic time for the donor organ. In addition, many children are sensitized from previous blood transfusions and may require exchange transfusions or plasmapheresis just prior to surgery. Standard anesthetic techniques for cardiac surgery are employed. As failure of the donor right ventricle postcardiopulmonary bypass is not unusual, attention needs to be focused on lowering the pulmonary vascular resistance and inotropic support (dopamine, epinephrine, milrinone) of ventricular function (64). Nitric oxide is a useful adjunct, and occasionally placing the patient on ECMO to allow for myocardial recovery and normalization of pulmonary artery pressures and resistance is necessary in the setting of actual or impending right ventricular failure.

Children presenting for re-transplantation are a combination of all these challenges (poor cardiac function from acute or chronic rejection, history of multiple previous surgeries, sensitization, etc.) plus the altered physiology of the transplanted heart and the

Anesthesia for pediatric cardiac transplantation

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Children presenting for re-transplantation are a combination of all these challenges (poor cardiac function from acute or chronic rejection, history of multiple previous surgeries, sensitization, etc.) plus the altered physiology of the transplanted heart and the
side effects of the immunosuppressive therapy on various organ systems.

Summary
Recent advances in donor allocation, critical care management, and immunosuppressive therapy have led to increased survival after pediatric cardiac transplantation: The 50% survival rate for infants is currently 18 years and will most likely continue to improve. In the pediatric population, the indications for heart transplantations have slightly shifted over the years: away from ‘irreparable’ congenital heart defects in infants toward CM and increasingly to ‘failed’ repairs or palliations in older children or adolescents. Unfortunately, the mortality on the waiting list is still very high: ~20%, emphasizing the need for further changes in the organ allocation and new ‘bridging’ solutions like ventricular assist devices. Finally, improving transplant morbidity by finding the perfect balance between effective immunosuppression and acceptable long-term side effects will be the major challenge for the coming years.

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REVIEW ARTICLE

Cardiomyopathy and heart failure in children: anesthetic implications

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Introduction

This review will include definitions and descriptions of cardiomyopathy and heart failure in children. The epidemiology and etiology of the more prevalent causes of heart failure, pathophysiology of specific cardiomyopathies, and common therapies in use today will be described. Important implications for anesthetic management will be highlighted.

Classification of cardiomyopathy and heart failure

Cardiomyopathy is a condition in which there is an abnormality of the myocardium. The most commonly used nomenclature used to describe the types of cardiomyopathy was developed by the World Health Organization (1). Accordingly, cardiomyopathies are classified according to etiology and physiology as (i) dilated cardiomyopathy (DCM), (ii) restrictive cardiomyopathy (RCM), (iii) hypertrophic cardiomyopathy, (iv) arrhythmogenic right ventricular cardiomyopathy, and (v) unclassified. Within these broad categories are more specific etiologies such as the viral inflammatory DCM more typically referred to as myocarditis (Figure 1).

Heart failure is characterized by reduced cardiac output and increased venous pressure in the systemic and/or pulmonary venous system. Progression of the disease occurs via myocyte dysfunction, myocyte death, and pathologic changes in the extracellular matrix. Heart failure, in turn, causes both circulatory and endocrine abnormalities. While congestive heart failure is frequently associated with cardiomyopathy, the two terms are not synonymous. Cardiomyopathy may exist without overt heart failure, and heart failure may occur in the absence of cardiomyopathy.

While the categorization of cardiomyopathy is aimed at distinguishing important anatomic and etiologic subtypes, the classification of heart failure focuses primarily on the severity of illness. One of the oldest classification systems, the New York Heart Association Class (NYHA), remains useful even today. The levels of severity in NYHA correlate moderately well with both prognosis and biomarkers such as circulating levels of norepinephrine (2,3). The NYHA classification

Keywords

cardiomyopathy; heart failure; pediatric anesthesia

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ranges from I (asymptomatic) to IV (heart failure symptoms at rest) (Table 1). Designed for adult patients, this scale has also been applied to children (4). The Ross Heart Classification Scale, with severity also ranging from I to IV, may be used in infants (5). An updated classification scheme that incorporates intensity of medical therapy was developed in 2001 and adapted for children in 2004 (Table 2) (6,7). Heart failure Stage A refers to the subset of the population with grossly 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 overload on the ventricle. Stage B is a presymptomatic state in which there is discernible myocardial dysfunction, including chamber enlargement or reduced systolic function. Patients in Stage B have never had signs or symptoms of heart failure. Stage C is marked by a present or past state of symptomatic heart failure. Stage C includes patients with 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. Stage D refers to patients with advanced heart failure requiring specialized therapy such as intravenous inotropes or mechanical circulatory support.

**Epidemiology**

A number of large studies describe the prevalence of DCM and of heart failure in children. Arola et al. (8) described a prevalence of idiopathic DCM of 2.6 per 100,000 children in Finland, with an annual incidence of 0.34 cases per 100,000 population. Nugent et al. (9) cited an incidence of 1.24 cases of new cardiomyopathy per 100,000 children <10 years of age in Australia. Of these cases, 58% were DCM and 26% were hypertrophic cardiomyopathy. Towbin et al. (10) published similar data in the United States, with an overall incidence of DCM of 0.57 cases per 100,000. This study demonstrates a markedly increased incidence in infants (4.4 cases per 100,000). Hypertrophic cardiomyopathy in children has a lower disease incidence of 0.32 cases per 100,000. RCM is rarer still, with an estimated prevalence of 0.03 per 100,000 children.

Another way to determine the population frequency of heart failure is to examine the frequency with which heart transplantation is performed in children. These data are tracked by both United Network for Organ Sharing (UNOS) and a multicenter research database, the Pediatric Heart Transplant Study (PHTS). The PHTS annual report shows that approximately 350 heart transplants are performed annually in children in the United States (11). The two most common groups of diagnoses leading to heart transplantation are cardiomyopathy and congenital heart disease (all types combined) (Table 3). The frequency of these two diagnoses varies by age but together they account for over 90% of all pediatric heart transplants.
Pathophysiology of heart failure

The sequence of heart failure begins with myocyte injury because of a congenital cardiomyopathy or underlying structural disease. The initial injury results in a reduction in cardiac output that is, in turn, countered by two major defense mechanisms. The first of these is intrinsic catecholamine stimulation. Catecholamine secretion has the early effect of increasing myocardial contractility and, via peripheral vasoconstriction, redirecting systemic blood flow to critical organs, including the heart. Enhanced catecholamine secretion, however, leads to further myocyte injury, dysfunctional intra-cellular signaling in response to beta-adrenergic stimulation, and ultimately myocyte death. The second important ‘compensatory’ mechanism elicited by circulatory insufficiency is the stimulation of the renin–aldosterone–angiotensin system (RAAS). The elevation of both aldosterone and angiotensin II promotes cardiac fibrosis and apoptosis. These mechanisms may temporarily contribute to circulatory stability, but over time become maladaptive and promote the progression of heart failure.

On a local organ level, diminished myocardial contraction in cardiomyopathy leads to reduced ejection fraction and chamber enlargement. As a consequence of the increased diameter of the heart, coupled with approximately stable wall thickness, there is a dramatic increase in systolic wall stress that leads to oxygen supply–demand mismatch in the myocardium. In some patients, enlargement of the ventricle leads to insufficiency of the atrioventricular valve and imposes a volume load on the already stressed myocardium. This, too, is maladaptive and leads to disease progression.

The mechanisms described earlier apply to all forms of DCM and do not appear to depend upon the underlying etiology (infectious, genetic, toxic, etc). It is likely that these same mechanisms operate in the setting of congenital heart disease with reduced systolic function, although research in this area is incomplete. The diseases of RCM and hypertrophic cardiomyopathy, however, are associated with very different pathophysiology. In RCM, the systolic function of the heart is typically preserved. Diastolic function is impaired, leading to elevated atrial pressure. Pulmonary congestion occurs when the left atrial pressure is elevated, and hepatic and renal dysfunction occurs when the right atrial and systemic venous pressures are increased. Cardiac output is quite limited in the setting of advanced RCM, in which there is a limitation in stroke volume because of the impaired diastolic filling. The major clinical problems with hypertrophic cardiomyopathy are not generally those related to heart failure per se, but rather dysrhythmias. The reader is referred to other reviews for further details regarding hypertrophic cardiomyopathy (12).

Outpatient treatment

In the current era, the outpatient treatment of heart failure is based on several clinical endpoints. The guidelines for heart failure management in children published by the International Society of Heart and Lung Transplantation offer detailed assessment of the evidence base for the practices described later (11).

The first treatment strategy for heart failure is to establish a euvolemic state through a combination of fluid restriction and diuretic therapy. This achieves symptom relief and also promotes good function of the major organ systems. This treatment, however, has no direct influence on the rate of progression of heart failure. Furosemide is the diuretic most commonly used for this purpose in children because of its relatively predictable action.

The second therapeutic option is to inhibit the RAAS pathway. This is critical to slowing disease progression. In adults, the efficacy of this approach has been proven in multiple large randomized clinical trials (13–15). No such randomized trials have been made in children, although it is generally believed that the RAAS pathway plays an important role in heart failure in children as well. The class of medications most commonly used for RAAS blockade is the angiotensin converting enzyme (ACE) inhibitors. These medications also cause arteriolar vasodilation and afterload reduction for the diseased myocardium. Afterload reduction, however, is not the major benefit from ACE inhibitor therapy, as was shown in the V-HEFT II trial (14). In this study, enalapril was compared with hydrazine, a nonselective vasodilator. Despite the comparable degrees of vasodilation, the group treated with enalapril had better outcomes, with a reduction in mortality of 30%. As an alternative to ACE inhibitors, angiotensin receptor blockers may produce similar effects. Finally, the use of medications such as spironolactone

| Table 3 | Diagnosis of heart transplant recipients (16) |
|-----------------|-----------------|-----------------|-----------------|
| Etiology        | Recipient age <1 year (%) | Recipient age 1–10 years (%) | Recipient age 11–17 years (%) |
| Cardiomyopathy  | 31               | 55               | 24              |
| Congenital heart disease | 63 | 36               | 64              |
| Retransplantation| 1                | 6                | 7               |
| Other           | 5                | 3                | 4               |
Heart failure in children: anesthetic implications

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or eplerenone to produce blockade of aldosterone has been proven efficacious, including in patients treated with ACE inhibitors (16).

A third option for outpatient heart failure therapy is the use of beta-receptor antagonists. Chronic elevations in plasma catecholamine concentrations cause heart failure progression via direct myocyte toxicity. Accordingly, circulating norepinephrine is a potent predictor of patient mortality. Beta-receptor antagonists afford the opportunity to effectively block this mechanism and thereby retard disease progression, or in some cases, to allow for significant degrees of cardiac recovery (17–19). However, implementation of this therapy may worsen heart failure by elimination of a critical element of circulatory support. It is, therefore, necessary to begin treatment with low doses of beta-blockers (e.g., propranolol, carvedilol) and titrate upwards slowly over a period of weeks to months. During heart failure exacerbations and inpatient treatment, it may be necessary to taper or discontinue beta-blockade.

Inpatient treatment

Children who require outpatient therapy for heart failure often require hospitalization owing to disease progression or temporary exacerbations of heart failure. Intravenous inotropes and vasodilators (or inodilators) are the mainstay of initial therapy, serving to restore adequate perfusion pressure and systemic oxygen delivery. The agents selected are often specific to institutional practice patterns: milrinone (a phosphodiesterase inhibitor), dopamine (a mixed alpha- and beta-agonist), and dobutamine (a beta-agonist) are among the more frequently used medications. Reduction in metabolic demand via mechanical ventilation is another method of support. Several types of mechanical circulatory support are employed to ‘bridge’ the heart failure patient to transplantation when more conventional therapies have failed.

Mechanical circulatory support therapies have evolved rapidly over the past decade for both adults and children. In 2006, Blume described the use of mechanical circulatory support in a 10-year period across the United States, including 99 of 2300 patients who subsequently had cardiac transplantation (20). More recent UNOS data are that 12% of children under age 12 years and 20% of teenagers have been treated with mechanical circulatory support while awaiting heart transplantation. This percentage continues to increase with the availability of devices such as the Berlin Heart EXCOR, which is suitable for children as small as 3 kg. Adults are increasingly treated with mechanical circulatory support either as ‘bridge to transplant’ or ‘destination’ therapy, i.e., with no plan of performing heart transplantation. This trend also applies to pediatric patients with severe heart failure. Such patients may have apparently stable circulatory dynamics but are anticoagulated and at risk of severe bleeding associated with surgical procedures. Additionally, cardiopulmonary resuscitation in such patients is hazardous and poses a risk of dislodging the intra-cardiac and intra-aortic cannulae. Children treated with mechanical circulatory support devices constitute a novel group of patients with unique treatment requirements.

Anesthetic management

Preoperative considerations

When evaluating the outpatient with heart failure, anesthetic concerns arise both from heart failure itself and its treatment. Even ambulatory heart failure patients can have low blood pressure at baseline as a result of the combined effects of disease, diuretic therapy, ACE inhibition, and beta-blockade. These conditions may predispose to severe hypotension following the administration of anesthetic agents. In addition, carvedilol, which is one of the commonly employed beta-blockers, has been shown to reduce the endogenous chronotropic and vasodilatory responses to anesthesia (21). Patients who are receiving comprehensive outpatient therapy are likely to have intravascular hypovolemia at baseline and this will be exacerbated by any period of preanesthetic fasting. These patients may become acutely hypotensive as a result of anesthetic-induced vennodilation, which can produce unexpectedly large decrements in cardiac preload. Patients with poor systolic function and marked degrees of ventricular enlargement may have relatively normal vital signs and physical examination but have acute deterioration following anesthetic exposure. Initiation of low-dose inotropic therapy prior to anesthetic induction may be warranted; this facilitates an increase in administration rate in the event of decreased cardiac output during the anesthetic.

It is crucial that the preprocedure anesthetic assessment include a detailed history, including exercise tolerance, prior anesthetic records, medications, and most recent laboratory assessments, including echocardiography. Direct communication between the treating cardiologist and the anesthesiologist should transpire proximate to the time of administration of anesthetic agents. Through this communication, the patient’s clin-
All of the volatile anesthetic gases depress myocardial contractility, especially in the newborn (31). Isoflurane and sevoflurane lower SVR and, therefore, blood pressure. The net effect on cardiac output may depend on preload and concomitant use of other cardio- and vasoactive agents. These agents do not appear to significantly change the ratio of pulmonary-to-systemic blood flow in patients with shunt lesions. In children with single ventricle physiology and stable ventricular function, sevoflurane at concentrations up to 1.5

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minimum alveolar concentration does not decrease myocardial performance index (32,33). The volatile agents may produce an increase in heart rate in normal children, especially during induction and during light anesthesia with or without surgical stimulation. The effects of volatile agents have not been well studied in children with heart failure. Even low concentrations of volatile anesthetics may cause severe hypotension in this population because of myocardial depression and reduction in SVR, both of which may be associated with decreased coronary perfusion and progressive compromise in cardiac function.

**Nitrous oxide**

There is little information regarding the effects of nitrous oxide in children with congenital heart disease and those with heart failure. Adverse effects of the addition of nitrous oxide to volatile anesthetics may well be attributable to the increased depth of anesthesia, i.e., equivalent increases in the concentrations of inhaled anesthetics have at least as much cardiodepressant effect. In general, nitrous oxide appears to have little effect on heart rate, cardiac contractility, pulmonary vascular resistance, and SVR compared with other agents administered in equi-anesthetic doses.

**Opioids**

Several publications have shown that high-dose opioids, including fentanyl and sufentanil, have minimal adverse effects on cardiac function and blunt the adverse stress response to surgery in infants. Remifentanil may be useful because its short onset and offset allow careful titration. In children without end-stage heart disease, remifentanil doses up to 0.1 \( \mu g \cdot kg^{-1} \cdot min^{-1} \) IV may be administered to spontaneously breathing patients during painful procedures (e.g., cardiac catheterization) with maintenance of circulatory function and without excessive respiratory depression (34). Histamine release associated with morphine administration in some patients may cause undesired decrease in preload and/or SVR. Caution must be applied to the use of large doses of all opioids in children with severe heart failure. Adverse effects may include slowing of the heart rate and a reduction in sympathetic tone in general, either of which may provoke exacerbation of heart failure in this population. The concomitant use of sedative agents, e.g., benzodiazepines, increases the risk of circulatory depression. Studies of combination drug therapy in children with heart failure have not been carried out.

**Dexmedetomidine**

The role of dexmedetomidine in anesthetizing children with heart disease, especially those with heart failure, remains unclear (35). Although this drug may allow for reduced doses of other maintenance agents, including inhaled agents, propofol, ketamine, and opioids, undesired slowing of the heart rate may occur because of the effects on cardiac conduction (36). This may be particularly deleterious in children with limited stroke volume in whom cardiac output may be relatively dependent on heart rate. The efficacy of adding dexmedetomidine to a propofol-based regimen for maintenance of anesthesia has been questioned (37).

Kipps et al. (38) reviewed records from 26 children with heart failure undergoing 34 procedures between 2002 and 2005. Only children with fractional shortening \( \leq 28\% \) were included, so that few patients with RCM and arrhythmogenic right ventricular cardiomyopathy were studied. Patients were categorized as having mild (fractional shortening [FS] 23–28\%), moderate (FS 16–22\%), or severe (FS <16\%) systolic dysfunction. All patients were receiving one or more medications for heart failure. The pediatric cardiac anesthesia team managed 85\% of the patients, including all of those with structural heart disease or idiopathic cardiomyopathy. The anesthetic management varied according to the severity of disease. The majority of children had anesthesia induced with ketamine or etomidate. Maintenance was achieved with propofol and ketamine or a volatile anesthetic agent. While 5 of the 13 procedures in patients with mild or moderate ventricular dysfunction were discharged home on the day of the procedure, all of the procedures in those with severe dysfunction were hospitalized afterward. Fourteen of these 21 patients were admitted to the intensive care unit, including 10 who were outpatients or admitted to the regular inpatient care unit prior to the procedure. Complications were noted in 38\% of the 34 procedures, primarily (83\%) in those with severe dysfunction. The most common complication was hypotension requiring vasoactive drug administration. One death occurred in a 16-year-old boy with severe DCM after the development of hypotension followed by cardiac arrest during placement of a biventricular pacemaker.

**Conclusions**

Infants and children with heart failure or cardiomyopathy represent one of the most challenging groups presenting to pediatric anesthetists. Some controversy exists as to whether pediatric cardiac anesthetists...
should care for all of these patients. Attention must be focused on preparation of the anesthetizing location, ensuring that resuscitation drugs are prepared in appropriate concentrations prior to the arrival of the patient. For all but the mildest of cases, intravenous induction should be undertaken with consideration of administration of small doses of hypnotic agents to ascertain a ‘dose–response’ with respect to blood pressure. In the highest risk patients, placement of an arterial catheter prior to induction should be considered utilizing local anesthesia with or without a small dose of an anxiolytic drug. Prior to the administration of any anesthetic agents, there should be discussion with the physician performing the procedure aimed at confirming the need for anesthesia (and the procedure) and minimizing the duration of the procedure. When appropriate, arrangements should be made for cardio-pulmonary bypass (or ECMO) back-up in the event of development of a life-threatening low cardiac output state.

References


Introduction

Heart failure in children is a diverse condition that can result from a variety of disease states including ‘simple’ and ‘complex’ congenital heart defects, various forms of cardiomyopathy, and myocarditis. The condition is not rare with over 12,000 pediatric hospital admissions for heart failure in the United States annually (1). Approximately 20% of these children have a cardiomyopathy and almost 60% have some form of congenital heart disease (Table 1). Among patients with congenital heart disease, defects range from ‘simple’ left to right shunting lesions found in two-thirds of patients to single ventricles found in approximately 10% of patients. This diversity of diseases accounting for heart failure admissions increases the complexity of care for these patients. While medical therapy is sufficient for many of these patients, some form of cardiac surgical or interventional procedure is performed in one-third of patients. These include late Fontan conversions (2), mitral valve annuloplasty, partial ventriculectomy in children, and endoventricular circular patch plasty in adults (3).

Only the minority of patients fail medical or surgical intervention and requires the use of extracorporeal membrane oxygenation (ECMO) (2%) or ventricular assist devices (VADs) (0.7%) performed in patients with the most severe disease. The first description of VAD use in children was in 1989 (4). In the 1990s, VAD use in children was sporadic. However, owing to improvements and miniaturization of equipment, VAD implantation in children has grown exponentially in recent years (5). The use of VADs is increasing in children (6,7) and likely will continue to progress as the availability and success of suitable devices increases (8). Similar to adults, VAD support in children could be used as a bridge to recovery, cardiac transplantation, and, eventually, as destination therapy in the foreseeable future. As these children survive longer with VAD support, awaiting organ availability, they will undergo multiple diagnostic imaging studies, interventions and noncardiac surgical procedures that will require perioperative sedation and anesthetic care (9).
Patient selection and timing of intervention

The successful management of patients on mechanical circulatory support (MCS) begins with patient selection. Patients whose heart failure has progressed to cardiogenic shock with multi-organ system failure, especially in the setting of chronic heart failure, have a very poor prognosis with VADs (10). Thus, it is our strategy to place patients on support before this occurs. We have developed criteria for consideration of VAD therapy (Table 2), which consist of the presence of refractory heart failure with inotrope dependence and at least one other organ system dysfunction.

The most common cardiac indication for circulatory support is failure to wean from cardiopulmonary bypass (CPB) after repair or palliation of complex congenital heart disease. There is no single diagnosis associated with the need of postoperative ECMO; however, in some series, single ventricle physiology and cyanotic heart lesions more commonly require support (11). The reported frequency of ECMO use after CPB in children is 1–5%. Left ventricular assist device (LVAD) is preferable over ECMO for patients suspected to need support longer (>2 weeks), who do not have pulmonary hypertension or respiratory dysfunction. However, for patient in acute decompensation and cardiac arrest, ECMO can be a lifesaving therapy.

Viral myocarditis is the leading cause of acute heart failure in children without congenital heart disease and is the most common indication of nonsurgical MCS. A recent review of the ELSO database in pediatric patients with acute myocarditis requiring MCS showed a 61% survival to discharge from the hospital (12).

Device selection is as important as candidate selection and timing of cardiac support. If the decision for MCS has been made, then we follow the algorithm in Figure 1, which is based on the etiology of the refractory heart failure.

![Figure 1 Algorithm for device selection at Texas Children’s Hospital](image)

**Table 1** Characteristics of children admitted for heart failure in the United States

<table>
<thead>
<tr>
<th>Heart failure patient characteristics</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total pediatric admissions 2003</td>
<td>12,683</td>
</tr>
<tr>
<td>Female</td>
<td>6,319 (60)</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>7,418 (59)</td>
</tr>
<tr>
<td>ASD, VSD, and/or PDA</td>
<td>4,911 (66)</td>
</tr>
<tr>
<td>Single ventricle, HLHS, tricuspid atresia</td>
<td>848 (12)</td>
</tr>
<tr>
<td>Other congenital heart disease</td>
<td>1,660 (22)</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>2,253 (18)</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>347 (3)</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>1,827 (14)</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>2,058 (16)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>1,082 (9)</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>675 (6)</td>
</tr>
</tbody>
</table>

Data from the 2003 Kids’ Inpatient Database.

ASD, atrial septal defect; VSD, ventricular septal defect; PDA, patent ductus arteriosus; HLHS, hypoplastic left heart syndrome. A person may have >1 diagnosis so the percentages will not add up to 100%.

**Table 2** Criteria for consideration of VAD as a bridge to transplantation

A pediatric patient with advanced heart failure should be considered for implantation of a VAD as bridge to transplant when the patient is listed for transplant or presumed to be a potentially acceptable candidate for transplantation and:

1. the patient has demonstrated inotrope dependency (worsening signs/symptoms of heart failure when inotropic support is weaned or withdrawn)

AND

2. there is evidence of compromise to at least one other organ system expected to recover with support:
   i. respiratory failure (e.g., requiring mechanical ventilation)
   ii. worsening renal function (e.g., rise in serum creatinine by at least 0.3 mg/dl)
   iii. hepatic dysfunction (e.g., AST >50 U·ml⁻¹, conjugated bilirubin >1.0 or INR >1.5)
   iv. inability to tolerate enteral feeds
   v. impaired mobility because of heart failure symptoms resulting in confinement to bed

OR

3. the patient is in cardiogenic shock or impending cardiogenic shock.

VAD, ventricular assist device.
shock can also be managed with these devices but recovery in this cohort should be expected within 5 days since it is well documented that support past this timeframe for postsurgical dysfunction has very poor outcomes. These short-term devices are a bridge to recovery or a bridge to decision. Assist devices are used as a bridge to recovery in children undergoing repair of congenital heart defects where the systemic ventricle may require a period of training, as following the arterial switch operation in older infants with d-transposition of the great arteries, or to allow resolution of myocardial edema or arrhythmias following a prolonged bypass. The use of MCS as a bridge for postcardiotomy recovery varies significantly between centers. We reported the rare use of MCS for this indication in our center over a 7-year period (6/2847 bypass procedures, 0.2%) with a 50% survival. However, others have applied postcardiotomy MCS as a routine following Norwood stage I repairs of hypoplastic left heart syndrome (average support of 3.1 days), with excellent hospital survival (89%) and near normal neurodevelopmental testing at 6-month follow-up. The bridge to decision occurs when a patient presents whose etiology of heart failure or its time course is unknown or their neurological status is in question. The bridge to decision children either recover so the VAD can be explanted or they do not recover and are transitioned to a long-term device if they are a transplant candidate (bridge to bridge strategy) or weaned to maximal medical support if they are not a transplant candidate.

If the cause of heart failure is chronic such as longstanding dilated cardiomyopathy or end-stage congenital heart disease, these patients are implanted with a long-term device as a bridge to transplant. For children with a body surface area (BSA) < 1.3 m², the Berlin EXCOR VAD (Berlin Heart AG, Berlin, Germany) is implanted. This is an air actuated paracorporeal VAD that is the only VAD being used in North America developed specifically for children. It can uniquely support children of all sizes and ages from 2.8-kg neonates to adult size children because it is available in six sizes. There are over 700 implants worldwide and over 300 in North America alone (Figure 2). The EXCOR is towards the end of its FDA IDE trial as a bridge to transplant only and has completed cohort one that are patients with a BSA < 0.7 m². The Berlin EXCOR allows for children to be mobile and rehabilitate physically and nutritionally as well as continue their development. For patients with a BSA > 1.3 m², we implant the Heart Mate II (Thoratec Corporation, Pleasanton, CA, USA), which is an intracorporeal small, noiseless axial flow device that presently is the most used LVAD in North America because of its low morbidity, especially with respect to thromboembolic events. Another advantage is that it allows quick rehabilitation and is FDA approved for hospital discharge. We have begun to discharge our patients from the hospital while they await transplant, which is a tremendous advantage socially and mentally especially for teenagers. The device can not only be used as a bridge to transplant, but since early 2010, it has been used as a destination therapy (bridge to destination). We have implanted the device in adolescents ranging from 12 to 17 years old, all of whom have survived to transplant and discharge.

Types of devices available for pediatric cardiac support

The use of MCS at Texas Children’s Hospital has increased dramatically over the past 15 years (Figure 3) with a changing makeup from a predominance of ECMO in the early era to an increase in the use of short- and long-term VADs such as the Tandem Heart and Berlin Heart EXCOR in the current era. Our center has favored the use of LVADs and avoid-
ing the use of a right sided device (RVAD) or ECMO whenever possible. This is based on the concept that even poorly functioning right ventricles can allow for filling of the LVAD if timing of support and management is optimized, and pulmonary vascular resistance (PVR) is managed appropriately (19). Additionally, LVADs with adequate management of RV function and PVR appear to have a survival advantage over the use of a biventricular device (BiVAD) at least among adult patients (10). Although we know from experience in care for children with single ventricular physiology that patients can survive for years without a subpulmonic pumping chamber (e.g. Fontan patients), a single ventricle is anatomically and physiologically different from a failing, dilated RV in the VAD setting. Varying degrees of right ventricular dysfunction are commonly present in patients with advanced heart failure and in the absence of mechanical support for the right ventricle, much of our medical therapy is aimed at support of the right ventricle (20).

Devices range from short-term acute support devices to long-term support with varied technology and flow characteristics. The most commonly used devices in North America are summarized in Table 3.

### Short-term MCS

**ECMO**

The most commonly used device in acute postcardiotomy or cardiac arrest states, an ECMO circuit is composed of a centrifugal or roller pump with a hollow fiber membrane oxygenator, oxygen blender, pump console and heat exchanger. Additional information about the ECMO equipment components is available at the ELSO web site: http://www.elso.med.umich.edu/.

**The RotaFlow**

A centrifugal pump without an oxygenator was suspended in three magnetic fields, allowing minimal friction and heat production. This results in almost immediate laminar flow and minimal damage to blood cells or activation of blood components. It is placed centrally with the inflow cannula in the left atrium and the outflow cannula in the aorta. This is our preferred device for patients needing temporary MCS who are <40 kg although it can be applied to patients of all sizes.

**Tandem heart**

For patient >40 kg especially those with prior sternotomy, the Tandem Heart is the preferred device. The Tandem Heart has favorable fluid dynamics because of
its hydrodynamic fluid bearing that supports the spinning rotor. The Tandem Heart is placed percutaneously through the femoral vessels. The Transseptal Extended Flow Cannula is placed through the femoral vein in the catheterization laboratory via a transseptal puncture into the left atrium. The arterial side is placed in the femoral artery. For children under 80 kg, we sew a vascular graft to the femoral artery and cannulate the graft so that the cannula never enters the artery itself, thus avoiding ischemia to the extremity.

**Long-term MCS**

See Figure 4.

**Berlin EXCOR**

Available in several pumping chamber sizes (10–80 ml), Berlin Heart VAD or EXCOR provides pulsatile flow delivered through a pneumatically driven thin membrane pump (14). In systole, the pump moves compressed air into the diaphragm causing the ejection. In diastole, negative pressure is generated to aid in the filling of the chamber. The maximum systolic positive pressure generated is 350 mmHg and the maximum negative driving pressure is minus 100 mmHg. It is a fixed volume, variable rate device. The pump rate can be adjusted between 30 and 150 beats-min⁻¹, and the systolic time can be adjusted between 20% and 70% of the cycle. The blood pump is transparent, allowing visual inspection of filling, emptying and thrombus formation. If there is any thrombus forma-

tion in the pump or cannulae, the pump must be exchanged to avoid systemic embolization. The blood-contacting surfaces of the pump including the polyurethane valves are heparin coated through the Carmeda process, reducing anticoagulation requirements. It also has silicon cannulae with a Dacron covering that works as a biologic barrier against ascending infections (Figure 5). When using this, VAD patients are not dependent on mechanical ventilation, can resume enteral feeding, are ambulatory and can be discharged from the ICU. The rate of neurologic complications of 5% is lower than ECMO and other adult-sized VADs (21).

**Heart Mate II**

Heart Mate II is an axial-flow LVAD. Axial flow devices are smaller and simpler than pulsatile pumps. They have only one moving component, with no valves, vent or compliance chamber reducing the complexity. Because of their small size, axial-flow LVADs can be used in smaller patients, BSA ≥ 1.4 m². Frazier published the first series using Heart Mate II in adult and teenage patients with an 81% survival rate (22).

**Thoratec**

Thoratec VAD (Thoratec Corporation) is a paracorporeal pneumatic VAD. The prosthetic ventricle has a 65-ml stroke volume chamber with a maximum output flow of 7 L-min⁻¹. It works on three different modes: fixed rate, synchronous (for weaning) or fill-to-empty mode. Like other paracorporeal pneumatic devices, it can be used as a LVAD or Biventricular VAD. The lower limits for implantation are a BSA of 0.7 m² and
an age of 7 year or older. Reinhartz reported a 68% survival to transplant or recovery in 209 pediatric patients (range 5–18 years, BSA 0.7–2.3 m²) (23). The risk of thromboembolism in children is higher than in adults because of the reduced flow velocities and blood stasis in the device owing to mismatch of the pump size to patient.

Noncardiac procedures in children on mechanical cardiac support

Children on MCS have a similar survival to transplantation and improved functional class similar to those transplanted without need for a bridge device (24). As the survival and duration of support improves, these patients require noncardiac interventions (9). In our series of Berlin EXCOR implants, 21 patients (mean age 42.7 months) underwent 62 noncardiac procedures (range 1–10 per patient), including imaging studies, otolaryngologic, general surgical and neurosurgical procedures and placement of PICC lines. The most common procedure was device exchange owing to detection of fibrin strands or clots. The risk of requiring a procedure correlated with the duration of support and not the device size.

Anesthetic considerations

The perioperative care and management strategy are dependent on the patient’s preoperative condition and comorbidities, intraoperative considerations and type of device placed.

Patient condition

These patients present for procedures with their underlying cardiac condition and its impact on end organ function, most importantly hepatic and renal impairment. Although the use of mechanical support has clearly been successful in improving the medical condition of these children, the use is not without the risk of significant morbidities that will affect the delivery of an anesthetic. The main risks appear to be central nervous system thromboembolic and bleeding; though, infections, abdominal complications and mechanical issues with the device are not trivial. While some studies have demonstrated good neurological outcomes in selected populations early after mechanical support the overall long-term neurocognitive outcomes of these patients is still largely unknown. However, limited data from ours and other centers has demonstrated a high incidence of impairments that should be considered before the delivery of an anesthetic for a noncardiac procedure (25,26). In a study of 42 survivors of MCS from our institution, 36% had moderate or severe motor or cognitive impairment at a median follow-up of 33 months after weaning from support (26).

Almost all children on MCS are at increased risk of consumption coagulopathy, and many are on a regimen of anticoagulant therapy ranging from unfractionated heparin, Enoxaparin, anti-platelet therapy (Dipyridamole or Aspirin) or Coumadin (27). Coagulation studies, medications, and blood transfusion requirements should be carefully considered preoperatively.

Intraoperative considerations

The response of children on MCS to various induction and maintenance anesthetic regimens has been examined in several case series (28–30). Hypotension occurred in 69% of a series of 11 Berlin EXCOR supported children, regardless of medication used and even at subtherapeutic doses (30). Preoperative stability was not predictive of intraoperative hypotension. In fact, only 17% of patients on preoperative inotropes experienced hypotension on induction of anesthesia compared to 41% of device supported children on no inotropes. The most important principle is the narrow therapeutic window of these patients’ tolerance to changes in venous or arterial capacitance using any induction agent. Ketamine induction and remifentanil infusion maintenance had the lowest incidence of hypotension. Hypotension was corrective with a fluid bolus (10 ml·kg⁻¹) in 60% of patients and an alpha receptor agonist (phenylephrine 1–5 mcg·kg⁻¹ bolus, norepinephrine, or vasopressin infusions).

Similar to the Thoratec, the Berlin EXCOR has a fixed chamber size, and both are considered fixed volume, variable rate devices. The rate of these devices is set (fixed) but can be adjusted and changed to improve perfusion. The Thoratec device will slow down in the presence of hypovolemia to allow the device chamber (65 ml) to fill. As stroke volume is significantly volume dependent in these devices, the most effective therapy for hypotension is fluid bolus and alpha-receptor agonists (31). Consideration for the effect of temperature, regional anesthetic techniques, and patient positioning on volume status are essential intraoperatively.

Increased pulmonary vascular resistance and right ventricular failure should always be considered and treated promptly in the presence of unexplained hypotension (32,33). Interventions to improve RV function include maintaining a mildly alkalaotic environment, use of phosphodiesterase inhibitors (milrinone), diuretics, and inhaled nitric oxide (iNO) or other pulmonary
dilators. Spontaneous ventilation lowers alveolar pressure and PVR, improves venous return and hemodynamic stability, and should be considered if the procedure allows.

Transesophageal echocardiography (TEE) is a useful guide not only during the initial device insertion, but also in other noncardiac procedures if applicable (34). Valvular disease can significantly affect device function. Mitral stenosis will limit device filling, while aortic or mitral insufficiency will cause back flow to the heart, thus limiting forward output and impeding LV unloading, resulting in LV distension, ventricular septal shifting, and RV failure. An adequately functioning device should result in minimal opening of the aortic valve, a decompressed LV chamber, and a midline septal position. TEE can also identify inflow cannula position, which should be aligned with the mitral inflow to produce laminar flow into the cannula. A peak mitral inflow velocity >2.3 m s⁻¹ is indicative of possible inflow cannula obstruction. RV function and PVR can also be assessed using TEE evaluation of septal position, chamber size, and degree of tricuspid insufficiency. Finally, TEE can also detect air entrainment through suture lines if the LV completely collapses and evaluate the presence of residual intracardiac shunting (a PFO) and assess the risk of systemic embolism.

Strict sterile techniques and bacterial endocarditis prophylaxis should be adhered to for all invasive procedures and whenever handling the devices. Blood stream infections can be fatal in these patients. Given the profound effects that nosocomial infections have on morbidity, mortality, and cost (35,36), all attempts are made to avoid central venous access if not needed for the procedure and to remove invasive lines as soon as possible. Placement of central venous lines must be carried out with careful positioning and caution to avoid the risk of venous air embolism from entrained air especially in patients with a vacuum-assisted diastolic filling device.

**Device type**

Understanding device technology is essential for managing children on MCS for noncardiac procedures. An appreciation of the various changes in the device output and the manipulations that can be made will help in treating hemodynamic changes during the delivery of a sedative or anesthetic. A perfusionist should

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**Table 4 Management of perioperative hemodynamic changes**

<table>
<thead>
<tr>
<th>Device</th>
<th>Hemodynamic change</th>
<th>Possible etiology</th>
<th>Device inspection</th>
<th>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 and incomplete fill in diastole</td>
<td>Fluid bolus (10 ml kg⁻¹)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Consider and treat promptly RV failure or ↑ pulmonary vascular resistance (PVR)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Increasing device rate not recommended as it will shorten fill time</td>
</tr>
<tr>
<td>Heart Mate II</td>
<td>Hypotension</td>
<td>Hypovolemia</td>
<td>Device flow will decrease (lowest 3 L min⁻¹ and rpm will slow (lowest 8000) beyond which device will shut until volume status corrected</td>
<td>Fluid bolus (10 ml kg⁻¹)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>✓ Consider and treat promptly RV failure or ↑ PVR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Alpha agonists (phenylephrine, norepinephrine) or vasopressin</td>
</tr>
</tbody>
</table>

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accompanied the patient during transport and remain accessible during the procedures. Table 4 describes some of the changes and interventions with the two most common long-term pediatric MCS devices in our practice.

In conclusion, the population of children with end-stage heart failure on MCS is growing. Anesthesiologists will become more involved in the care for these patients not only for device insertion or transplants but also for more noncardiac procedures, the longer and better they survive. A better understanding of patient demographics, device selections, and response to anesthetics is essential for the safe care for these children.

References


The term low birth weight (LBW) refers to infants born at a weight less than or equal to 2500 g. This group includes infants born preterm (gestational age <37 weeks) and those born at term but who are small for gestational age (SGA, defined as <3rd percentile for weight). Many SGA babies suffer from intrauterine growth restriction (IUGR). Risk factors for prematurity and SGA are similar, and up to 50% of extremely preterm neonates are SGA (1).

Premature babies are more that twice as likely to have cardiovascular malformations than infants born at term (2), and infants with congenital heart disease (CHD) have a high incidence (approximately 16%) of LBW (2–5).

Infants with CHD have an incidence of 13–20% of associated congenital anomalies or genetic syndromes (4–6), and many of these conditions are associated with IUGR. Thus, up to 30% of infants who are of LBW and have CHD have associated extracardiac anomalies, syndromes, or chromosomal anomalies (7,8).

When compared to term infants, LBW/premature infants were more likely to have pulmonary atresia with ventricular septal defect, complete atroventricular septal defect, coarctation of the aorta, tetralogy of Fallot, and pulmonary valve stenosis. Fewer LBW/preterm infants had pulmonary atresia and intact ventricular septum, transposition of the great arteries, and single ventricle (2).

Survival rates for open-heart surgery (OHS) in neonates have improved substantially over the last 10 years (9–12). However, LBW remains a risk factor for increased mortality and morbidity after open-heart surgery (OHS). There is a paucity of information about the anesthetic challenges presented by LBW infants undergoing OHS. This review summarizes the perioperative issues of relevance to anesthesiologists who manage these high-risk patients. Emphasis is placed on management concerns that are unique to LBW infants. Retrospective data from the authors’ institution are provided for those aspects of anesthetic care that lack published studies. Successful outcome often requires substantial hospital resources and collaborative multi-disciplinary effort.
and issues related to anesthesia, surgery and cardiopulmonary bypass (CPB) (22).

We were unable to find reports of the anesthetic challenges presented by LBW infants undergoing OHS. Therefore, we describe our approach at Stanford University’s Lucile Packard Children’s Hospital and present data from a retrospective review of our experience. The medical records of all children who underwent OHS during the period January 1, 2002 to April 30, 2006 were examined after obtaining Institutional Review Board approval and waiver of consent. Patients weighing 2.5 kg or less at the time of surgery were included in the study. Data concerning patient demographics, antenatal, and hospital course were recorded, with special attention to the perioperative period.

Timing and type of surgery

In the past, OHS was intentionally delayed for LBW infants. If surgical intervention was necessary, palliative procedures were performed rather than more extensive, complete repairs. The intention was to wait for the infant to attain greater weight and a more mature gestational age. These approaches have not been shown to improve outcome, and some studies suggest that intervening mortality is higher (8), and significant morbidities are associated with the delay (20). Nowadays, early primary repair is often preferred (13–17,22,23).

Preoperative concerns

Therapeutic strategies to optimize the patient’s cardiovascular status are lesion-specific and are as relevant to LBW infants, as they are to term infants of normal weight. The preoperative challenges unique to LBW infants are largely because of comorbidity. A retrospective review of 105 LBW infants undergoing cardiac surgery with or without CPB (patients with isolated patent ductus arteriosus were excluded) found median birth weight was 2130 g (range 431–2500 g), and median gestational age was 36 weeks (range 25–41.1 weeks). Of the group, 64% had been born prematurely, 27% were SGA, and 32% had associated major congenital anomalies (22). The Stanford series (all patients undergoing OHS) was similar (Table 1).

Concerns related to prematurity and SGA

Infants who are premature or SGA have increased risk of morbidity and mortality. The risk is even greater for those who are premature and SGA, presumably because an unfavorable in utero environment further compromises the patient’s immature organs (1). IUGR increases the incidence of respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), and retinopathy of prematurity (ROP) in premature babies (24–28). Tables 2 and 3 list the pathologies encountered commonly in LBW infants.

Pulmonary issues

Preterm infants have arrested lung development with impaired alveolarisation and dysmorphic vasculogenesis (29). Reduction in functional residual capacity (FRC) is independently associated with prematurity, IUGR, and severity of BPD (30). Premature infants with surfactant deficiency develop RDS; BPD is the end result of a variety of insults to the lungs, including lung immaturity, surfactant deficiency, oxygen toxicity, infection, poor nutrition, and mechanical ventilation. Improvements in ventilator management strategies, widespread use of surfactant, and prenatal administration of glucocorticoids have improved survival of premature infants and hence the prevalence of BPD (31,32). CHD results in a slower rate of recovery of pulmonary function in patients with BPD (33), and patients with CHD and BPD have signifi-

Table 1 Patient demographics (n = 65)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Valuea</th>
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</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
</tr>
<tr>
<td>LBW infants (&gt;1.5–2.5 kg)</td>
<td>56 (86)</td>
</tr>
<tr>
<td>Very LBW infants (&gt;1.0–1.5 kg)</td>
<td>6 (9)</td>
</tr>
<tr>
<td>Extremely LBW infants (&lt;1.0 kg)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Female gender</td>
<td>38 (58)</td>
</tr>
<tr>
<td>Weight at birth (kg, mean ± sd)</td>
<td>1.92 ± 0.51</td>
</tr>
<tr>
<td>Weight at surgery (kg, mean ± sd)</td>
<td>2.02 ± 0.44</td>
</tr>
<tr>
<td>Born at study institution</td>
<td>13 (20)</td>
</tr>
<tr>
<td>Age at admission to study institution (days, mean ± sd)</td>
<td>8 ± 14</td>
</tr>
<tr>
<td>Age at surgery (days, mean ± sd)</td>
<td>18 ± 20</td>
</tr>
<tr>
<td>Pregnancy and birth</td>
<td></td>
</tr>
<tr>
<td>Maternal age (years, mean ± sd)</td>
<td>28.7 ± 6.4</td>
</tr>
<tr>
<td>Parity (mean ± sd)</td>
<td>2 ± 1</td>
</tr>
<tr>
<td>Prenatal maternal complications</td>
<td>28 (43)</td>
</tr>
<tr>
<td>Fetal diagnosis of congenital heart disease</td>
<td>19 (29)</td>
</tr>
<tr>
<td>Premature infants (&lt;37 weeks gestation)</td>
<td>37 (57)</td>
</tr>
<tr>
<td>Gestational age (weeks, mean ± sd)</td>
<td>35 ± 3</td>
</tr>
<tr>
<td>Small for gestational age (SGA)</td>
<td>28 (43)</td>
</tr>
<tr>
<td>Premature + SGA</td>
<td>11 (17)</td>
</tr>
<tr>
<td>Twin or triplet</td>
<td>18 (28)</td>
</tr>
<tr>
<td>Apgar score at 1 min (mean ± sd)</td>
<td>7 ± 2</td>
</tr>
<tr>
<td>Apgar score at 5 min (mean ± sd)</td>
<td>8 ± 1</td>
</tr>
<tr>
<td>Genetic or congenital anomaly</td>
<td>16 (24)</td>
</tr>
</tbody>
</table>

LBW, low birth weight.

*Values expressed as n (%) unless stated otherwise.
cant morbidity and mortality compared with CHD patients without BPD (34). It is unclear whether palliating high-risk patients [increased pulmonary vascular resistance (PVR), severe BPD] in the early postnatal period until their pulmonary arterial and alveolar function has had an opportunity to recover is preferable to an early corrective procedure. However, palliation, including banding of the pulmonary trunk or shunting the pulmonary artery in the face of labile pulmonary vasculature, can pose serious problems in regulating pulmonary blood flow. Patients with BPD and univentricular hearts have a high risk of mortality (34). Abnormal capillary distribution and the presence of aortopulmonary collaterals in children with BPD may have significant implications for regulating pulmonary blood flow in palliated univentricular hearts (34).

Lung disease complicates the perioperative management of the infant with CHD as follows:

**Surfactant**
Premature infants with RDS and ongoing ventilator and oxygen requirements may require repeat doses of surfactant. In some cases, it may be difficult to determine whether the continued respiratory dysfunction is primarily pulmonary or cardiac in origin. Adverse effects of surfactant administration include pulmonary hemorrhage (particularly in patients with left-to-right shunt via a ductus arteriosus), endotracheal tube (ETT) obstruction, sinus bradycardia, blood pressure swings, and desaturation (35). The benefits from surfactant therapy need to be weighed against the risks of treatment. Premature infants are at risk for surfactant dysfunction, even after the initial RDS has resolved (36). Additionally, CPB may result in surfactant dysfunction in infants (37,38). It is unclear whether perioperative surfactant therapy improves patient outcome (35). At Stanford, it is reserved for instances of severe perioperative RDS.

### Table 2 Premature infants: postnatal clinical concerns

| Small size | Procedures technically challenging, specialized equipment required |
| Respiratory system | Birth asphyxia, Respiratory distress syndrome, Chronic lung disease (bronchopulmonary dysplasia), Apnea of prematurity, Subglottic stenosis, Increased incidence of congenital respiratory system anomalies |
| Cardiovascular system | Persistent fetal circulation, Patent ductus arteriosus, Persistent pulmonary hypertension, Increased incidence of congenital cardiovascular anomalies |
| Central nervous system | Intraventricular hemorrhage, Hypoxic-ischemic injury before, during, and after birth, Retinopathy of prematurity, Neurological injury at lower bilirubin levels |
| Gastrointestinal system | Jaundice from reduced hepatic conjugation of bilirubin, Necrotizing enterocolitis, possibly resulting in short gut syndrome, Hepatotoxic agents (e.g., parenteral nutrition), Increased risk of congenital gastrointestinal anomalies |
| Genitourinary system | Fluid and electrolyte abnormalities, Increased exposure to hypoxia, hypoperfusion and nephrotoxic agents, Increased risk of congenital genitourinary anomalies |
| Infection | Increased risk of infection from mother, indwelling catheters, endogenous gut flora, hospital environment |
| Nutrition and metabolic | Increased risk of hypo- and hyperglycemia, Vitamin K, iron deficient, Reduced serum bicarbonate, therefore reduced buffering of acid |
| Temperature and humidity | Increased risk of hypothermia and hyperthermia, Prone to dehydration from transdermal water loss |
| Hematology | Anemia (from prematurity, blood sampling, iron deficiency, disease-e.g., sepsis), Polycythemia (cyanotic heart disease), Thrombosis (intravascular catheters, dehydration, low cardiac output), Bleeding (vitamin K deficient, thrombocytopenia, disease-e.g., sepsis) |
| Endocrinology | Insufficiency of thyroid and adrenal hormones |
| Pharmacology | Polypharmacy with potential for drug toxicity, adverse reactions, drug interactions, and medication errors |

### Table 3 Small for gestational age infants: Postnatal clinical concerns

| Perinatal asphyxia; sequelae include | Hypoxic-ischemic encephalopathy, seizures, Aspiration pneumonia, Myocardial dysfunction, Acute tubular necrosis of the kidney, Necrotizing enterocolitis, Liver dysfunction, Adrenal insufficiency because of hemorrhage, Disseminated intravascular coagulation, Meconium aspiration syndrome, Persistent pulmonary hypertension of the newborn, Pulmonary hemorrhage, Hypoglycemia, Hyperglycemia, Polycythemia/hyperviscosity, Temperature instability |

Modified from Rosenberg A (1).
**Lung compliance**
Surfactant therapy, resolving RDS, and evolving BPD alter pulmonary compliance and thereby affect pulmonary blood flow. This complicates the maintenance of balanced pulmonary and systemic circulations in patients with cardiac shunt. The inflammatory response elicited by OHS may adversely affect a previously damaged lung (39). LBW infants may have limited defenses to free radical damage sustained during CPB (40).

**Airway resistance**
Elevation in airway resistance may be because of bronchial vessel compression, bronchial compression by enlarged pulmonary arteries, ischemic tracheal segments after surgery to unifocalize aortopulmonary collaterals, accumulation of secretions and bronchial reactivity, particularly after CPB (39,41–49). The airway may be compromised by congenital anomalies (e.g., complete tracheal rings) or acquired subglottic stenosis from previous endotracheal intubations.

**Mechanical ventilation**
The stresses imposed on premature lungs by mechanical ventilation are implicated in the arrest of normal lung growth seen with RDS and the severity of subsequent BPD. For neonatologists, a primary goal during mechanical ventilation is the avoidance of ventilator-induced lung injury (VILI). The strategies employed in most NICUs emphasize stabilizing FRC with positive end-expiratory pressure (PEEP), minimizing ‘volutrauma’ by using small tidal volumes (e.g., 4–5 ml·kg⁻¹), minimizing inspiratory times (0.35 s or less) to avoid an I : E-ratio > 1 : 1, and increasing rate as needed to maintain a PₐCO₂ consistent with mild ‘permissive hypercapnia’ (50–53). The ultimate expression of this strategy is high-frequency ventilation; FRC is maintained by PEEP or mean airway pressure, and rapid tiny volume breaths are used for ventilation. Even a few large tidal volume breaths have been shown to be injurious to newborn animal lungs (53–56). For these reasons, neonatologists commonly are averse to bag-mask ventilation, especially given the inaccuracy of analog manometers (57). At Stanford, we are moving to the use of flow controlled, pressure limited mechanical devices specifically designed for neonatal resuscitation and short-term ventilation.

Postoperative cardiac patients are typically ventilated using high tidal volumes, low rates, and variable amounts of PEEP. This strategy minimizes effects on right heart afterload, but these higher tidal volumes place immature lungs at high risk for VILI. Ades and colleagues suggest transitioning postoperatively to NICU ventilation strategies as soon as hemodynamics permit (35). PEEP or continuous positive airway pressure helps maintain FRC, preventing atelectasis, improve ventilation/perfusion matching, and stabilize the premature’s highly compliant chest wall. However, caution is necessary because overdistension of the lung will impede venous return, increase PVR, and potentiate lung injury. Unfortunately, the prolonged ventilator support required by patients with BPD increases the risk of subsequent morbidity (34).

Apnea of prematurity is common in infants <32 gestational age and may complicate postoperative withdrawal of mechanical ventilation. Of note, caffeine, initially used to treat apnea of prematurity, has been shown to decrease the incidence of BPD and improve neurological outcome (58).

**Carbon dioxide**
Permissive hypercapnia is a common mechanical ventilation strategy to limit BPD in LBW infants. However, hypercapnia may perturb hemodynamics by inducing pulmonary vasoconstriction, systemic vasodilation, and decreased cardiac function. This may be especially relevant post-CPB, when there may already be elevated PVR and myocardial dysfunction. Preoperatively, permissive hypercapnia is preferentially employed at our institution to balance systemic and pulmonary blood flow in patients with mixing lesions because it augments cerebral blood flow (59). Most investigators believe that permissive hypercapnia within reasonable limits (e.g., PₐCO₂ < 55 initially, slightly higher if adequate pH compensation) (60,61) does not increase the risk of intraventricular hemorrhage (IVH). However, extreme hypercapnia, and marked swings in PₐCO₂, may be associated with increased IVH rates (62,63). Both extremes of arterial carbon dioxide pressure and the magnitude of fluctuations in arterial carbon dioxide pressure are associated with severe IVH in preterm infants (64,65).

**Oxygen**
Oxygen administration to the preterm infant is suspected to cause tissue damage via oxygen-free radicals and is implicated in BPD and ROP (66). The antioxidant system is compromised in prematurity, as hydroxyl radical formation is increased beyond the immature infant’s capacity to limit oxidative damage (67). Biochemical markers of oxidative stress are still elevated 28 days after birth in newborns resuscitated with 100% oxygen compared with those who received room air (68). The International Liaison Committee on Resuscitation stated air is as effective as 100% oxygen for the resuscitation of most infants at birth (69). A United Kingdom survey found no consistency in the use of oxygen during anesthesia in premature and newborn...
infants (70). For LBW infants with CHD, the desired oxygen saturation levels to avoid pulmonary over-circulation in ductal-dependent lesions and those obtainable in cyanotic heart lesions are similar to the saturations recommended to minimize oxygen toxicity in premature infants. In other cardiac lesions, maintaining this lower saturation goal should not be harmful (57). Near infrared spectroscopy (NIRS) monitoring of cerebral saturations may be helpful in guiding oxygen therapy. Oxygen administration will decrease PVR in some patients with pulmonary hypertension (PHT).

ROP is found primarily in preterm infants <32 weeks gestational age and results from abnormal development of the retinal vasculature. In Phase I of the disease, oxygen levels in the preterm infant’s retina are higher than normal in utero values, and this relative hyperoxia impairs retinal vessels growth. This is followed in Phase II by hypoxia-driven uncontrolled abnormal vessel growth. Evidence is accumulating that one of the strongest predictors of ROP, in addition to low gestational age, is poor weight gain during the first weeks of life (71–73), and a common mechanism is proposed (74). During the third trimester, physiological ‘hypoxia’ of the retina stimulates vascular endothelial growth factor (VEGF) secretion. VEGF requires insulin-like growth factor I (IGF-I) to initiate normal retinal vasculatisation (75). IGF-I is essential for both pre- and postnatal general growth as well as for growth of the retinal vasculature, and serum levels are low in the premature (76). Thus, the relative retinal hyperoxia of extra-uterine life (compounded by supplemental oxygen) and the deficiency of IGF-I combine to prevent normal retinal vessel growth. Postnatal growth retardation is a major problem in very preterm infants, especially if they have CHD. Poor early weight gain and low serum IGF-1 levels both correlate with severity of ROP (73,77). This may explain the observed association between ROP and CHD. A meta-analysis found that restriction of oxygen significantly reduced the incidence and severity of ROP without increasing death rates (78), although increased mortality remains a concern (79). Many units will now tolerate SpO2 levels in the 70–90% range for premature infants during their acute illness (80), while a higher SpO2 range may be indicated during Phase II of ROP (81). Therefore, for LBW infants with CHD, it seems reasonable to follow neonatal intensive care ROP guidelines, unless this conflicts with the needs of managing the physiology of the underlying defect.

There are virtually no data to guide oxygen management of the LBW infant during CPB. Variables such as hemodilution, CPB circuit primed with banked adult red blood cells, hypothermia, cerebral blood flow, and variations in pump flow and circuit volumes make it exceedingly difficult to maintain oxygen saturations in the range recommended for premature infants, and clinical outcome studies would be challenging. Our CPB management of oxygen administration in premature infants does not differ from our practice in term infants.

Cardiovascular issues

Systemic vascular resistance in the fetus is very low, with both ventricles contributing to systemic cardiac output. At birth, the left ventricular output approximately doubles. There are fewer contractile elements in the immature heart, and the myocardium is less compliant. This stiffness renders the ventricle relatively intolerant of volume and pressure loading. There is limited ability to increase stroke volume, and cardiac output is heart rate sensitive. Parasympathetic tone predominates. Hypotension is often noted in the preterm neonate and is commonly because of myocardial dysfunction or altered peripheral vasoregulation. The neonatal myocardium is more sensitive to changes in extracellular ionized calcium and relies more on glucose metabolism (compared with fat) than that of older patients. Thus, premature and SGA infants may be more at risk for myocardial dysfunction given their decreased stores of calcium, inadequate glycogen stores, and impaired gluconeogenesis (35). Alpha and beta adrenergic receptors in premature infants are adequate in number and function. However, coupling of adrenergic receptors to adenylate cyclase is incomplete and may render milrinone less effective. Unfortunately, inotropic agents have not been well studied in the preterm population, and data regarding safety and efficacy are lacking (82). Thus, choice of inotrope therapy is mostly determined by institutional practice. Hydrocortisone is an option for ‘pressor-resistant’ hypotension (83) or capillary leak syndromes, which are common in cardiac and premature infants. However, steroid therapy has been associated with adverse neurodevelopmental outcomes and bowel injury.

PHT can complicate the perioperative period in LBW infants undergoing OHS. Acidemia, hypoxia, CPB, and noxious stimuli can potentiate PVR. Certain cardiac and noncardiac congenital anomalies are at increased risk for PHT. Patients with single ventricle palliation do poorly when PVR is elevated. PHT is more likely in infants with BPD and, when present, is associated with higher mortality after OHS (34).

Gastrointestinal issues

Premature and SGA infants are at increased risk for necrotizing enterocolitis (NEC), a disease in which the
Renal issues

In children and infants, acute kidney injury incidence after OHS varies from 2.7% to 24.6% (95, 96), with survival rates ranging from 21% to 80% (97). Young age and small size were risk factors for poor renal outcome (98), and there are multiple reasons for this (97). Premature infants have lower glomerular filtration rates (GFR), higher renovascular resistance, and impaired concentrating and diluting abilities compared to term infants. The immature tubular function leads to bicarbonate and sodium losses, thus requiring replacement to maintain normal sodium balance and avoid acidemia. Adequate GFR is maintained by postglomerular, efferent arteriolar vasoconstriction, which mainly is dependent on a high level of angiotensin II and angiotensin-converting enzyme inhibitors should be used with caution (99). Similarly, prostaglandin synthase inhibitors administered to close a patent ductus arteriosus may blunt the vasodilation needed to maintain adequate perfusion of the LBW kidney. Hypoxemia, hypothermia, and sepsis-associated vasoactive substances (e.g., endothelin, thromboxane A2) reduce renal blood flow and GFR and activate the renin-aldosterone-angiotensin system. Both before and after surgery, low cardiac output syndrome was a major determinant of renal injury (95). Positive pressure ventilation decreases venous return and increases renal sympathetic nervous activity and serum vasopressin levels (97). LBW infants are often exposed to nephrotoxic agents such as antibiotics and intravenous contrast media. CPB impairs renal function by activation of inflammation, nonpulsatile flow, hemolysis, and ischemia. Circulatory arrest and duration of CPB are associated with acute kidney injury in infants (95). Recent reports have suggested that theophylline may be protective against renal injury in neonates with respiratory distress (100) and asphyxia (101). This has not been studied in the context of CPB, but the analogy could be made. Thus, theophylline may be considered a potential means of prophylaxis against postoperative renal dysfunction in infants undergoing OHS.

Neurological issues

Compared to normal weight infants, LBW infants are more likely to incur brain damage and have long-term neurological disabilities; this is especially true for the extremely LBW (<1000 g) child (102). Factors that are implicated include genetic disorders, brain injury in utero, perinatal asphyxia, IVH (associated with prematurity), and postnatal insults such as hypoxia, hypoperfusion, and infection. OHS during infancy is also associated with early and late neurological morbidities. Neurological complications such as stroke and seizures can present in the early postoperative period, but are less common than the longer-term issues such as cognitive and intellectual impairment, attention and executive function deficits, visual-spatial and visual-motor skills deficiencies, speech and language delays, and

Gut mucosal barrier is damaged by pathogenic enteric bacteria and may progress to bowel necrosis, sepsis, and death. Coexisting CHD further increases the incidence of NEC (84). Risk factors include poor systemic perfusion, particularly if the cardiac anomaly causes substantial aortic run-off to the lungs (e.g., truncus arteriosus) and prostaglandin infusion rates > 0.05 mcg kg⁻¹ min⁻¹ (7, 84). NIRS monitoring of the anterior abdomen has been reported to be a valid noninvasive measure of splanchnic oxygen saturation in infants following OHS (85). Jaundice is more severe in LBW infants because of reduced red cell survival and liver immaturity. Preterm infants suffer brain damage at lower unconjugated bilirubin levels than term babies because of a relative deficiency of the protective substance P-glycoprotein and the increased exposure to exacerbating factors such as hypoxia, acidosis, hypercapnea, and hypothermia (86). Attention to the pre- and postoperative nutritional requirements is vital for LBW infants undergoing OHS. The complications of intravenous hyperalimentation can be severe and include line infections, thrombosis, and liver injury. Therefore, enteric feeding is preferable with the understanding that these patients are at risk for NEC and aspiration (increased incidence of gastrointestinal reflux and vocal cord paresis).

Neonatologists have been focusing attention lately on what has been termed ‘extra-uterine growth retardation’: the common phenomenon of poor growth for very low birth weight infants during their NICU stay (87–89). This failure to grow appropriately and maintain weight above the 10th percentile for postmenstrual age has been associated with a more complicated NICU course, and a worse long-term outcome (90). Providing more protein intake in the first week of life may at least in part ameliorate this; an extra gm per kg of protein daily during that time resulted in better growth and an 8.2-point improvement in Mental Development Index (91, 92). Thus, there has been an increased focus on providing more protein and calories starting immediately upon NICU admission up to 3 g·kg⁻¹ even on the first day of life (93, 94). Because premature infants with CHD frequently require various intravenous infusions (e.g., alprostadil, dopamine), there commonly is conflict between the desire to provide maximized parenteral nutrition and the need for fluid restriction.

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behavioral difficulties (103–105). Mechanisms of injury include patient-specific factors such as genetic predisposition, gender, race, socioeconomic status, and in utero central nervous system development. Modifiable factors include not only intraoperative variables (CPB, deep hypothermic circulatory arrest, and hemodilution) but also such variables as hypoxemia, hypotension, and low cardiac output (106). In addition, there are concerns about the possibility of anesthesia-induced neuronal cell loss in the developing brain (107–109). The strongest predictors of a worse neurodevelopmental outcome at 1 year of age were reported to be patient-specific factors including presence of a genetic syndrome, LBW, and presence of the apolipoprotein E genotype (110). A large, prospective cohort study demonstrated a 10% prevalence of stroke in infants with CHD undergoing OHS, half of which occurred preoperatively. LBW was independently associated with stroke (111).

Measures to protect the infant brain during OHS continue to evolve (103). There has been concern that the immature germinal matrix of premature infants would greatly increase the risk of IVH following OHS. However, the incidence of severe IVH in premature infants (median gestational age = 33 weeks) undergoing OHS was not different from a control group without CHD (7). Most cases of severe IVH present in the first 72 h after birth and occur in infants <30 weeks gestational age. Therefore, it might be reasonable to delay OHS beyond the first few days of life if the infant is very premature.

Other issues

Infection
Extremely premature newborns have a 5- to 10-fold higher incidence of microbial infection than term newborns (112). Infections decrease the chance of survival. Unfortunately, premature infants are more likely to be exposed to risk factors for infection such as indwelling vascular catheters, mechanical ventilation, intravenous hyperalimentation, NEC, invasive procedures, and prolonged hospital stay. Patients with conotruncal cardiac defects are more likely to have 22q11.2 deletion syndrome (DiGeorge anomaly) and be immunocompromized. Blood transfusions and steroid therapy may also depress immunity.

Thermoregulation
LBW infants at risk for hypo- and hyperthermia and dehydration because they have a larger body surface area/weight ratio, very thin skin, decreased brown fat are unable to shiver or sweat and assume a flaccid open posture. Body core temperature typically responds quickly to thermo-manipulation during CPB. Babies are particularly prone to becoming hypothermic during transport and in the operating room prior to draping for surgery when the child is fully exposed. Measures that help thermoregulation include transportation in an incubator, preparing the OR to appropriate temperature and humidity, heating lights, plastic wrap, warm, humidified inspired gases, and warmed topical and intravenous fluids.

Hematology
LBW infants are often anemic (immature marrow, low erythropoietin concentration, reduced red blood cell life-span, iron deficiency, frequent blood sampling). Their coagulation profile is different but adequate, with a tendency toward thrombosis – particularly if polycythemia, low cardiac output, or dehydration are present (113). It is pointless to treat clotting study results for a premature infant that may be in the ‘abnormal’ range for older children; ‘normal’ results will not be achieved, blood products will be wasted, additional fluid load will be given, and hypercoagulation may be the result. Additionally, erythropoietin studies for the treatment of anemia have demonstrated that premature infants tolerate quite well much lower hematocrits than was previously believed. Current transfusion recommendations for premature infants now are much lower, with hematocrits in the 18–20% range deemed acceptable by many (114).

Pharmacology
LBW infants may differ from term infants in dose response because of pharmacokinetic and pharmacodynamic effects. For example, there are differences because of organ immaturity (liver, kidney, gut), body composition (total body water, fat, protein binding, pH, bilirubin), and age-dependent metabolic pathways (e.g., theophylline) that affect drug metabolism and clearance.

Invasive therapies
Central intravascular catheters are often present. Positioning of the catheter tip should be checked because adverse events are more common at certain sites (e.g., renal thrombosis when umbilical artery catheter located at origin of renal arteries). Long duration in situ and urgency of placement usually raise our concern for catheter-associated infections.

Anesthetic management
Cardiopulmonary bypass
Table 4 lists details of surgery and CPB management of the Stanford LBW patients. Owing to a lack of
relevant data, CPB management of LBW infants is mostly extrapolated from experience gained caring for term neonates. This is suboptimal because CPB is different for LBW patients in the following aspects:

**Hemodilution**

Hemodilution is extreme, resulting in increased blood product requirements to correct anemia and coagulation function. Mean prime volume ranged from 1.8 to 6.5 times greater than the estimated blood volume of Stanford study patients. Miniaturized CPB circuits are being developed, but are not currently available for clinical use. Successful use of a nonheme prime for a 1700-g premature infant has been reported (115), but hematocrit values during CPB fell to values that others have associated with poorer neurological outcome (116).

**Inflammatory response to CPB**

Tremendous activation of inflammation can result in fluid exudates and substantial tissue edema. Often our surgeons opt for delayed closure of the sternum, and many LBW infants require insertion of a peritoneal dialysis catheter to avoid an abdominal compartment syndrome. In hope of mitigating the inflammatory response, we perform dilutional conventional ultrafiltration and usually remove 600–1000 ml of ultrafiltrate. Methylprednisolone (30 mg $\times$ kg$^{-1}$) and mannitol (0.5 g $\times$ kg$^{-1}$) are added to the CPB prime. The addition of modified ultrafiltration may be useful if the duration of conventional ultrafiltration is curtailed by an extended period of circulatory arrest (117).

**Oxygen toxicity**

As mentioned earlier, the optimal oxygen values during CPB are unknown. It would be technically challenging during CPB to provide adequate systemic and cerebral perfusion if SaO$_2$ was maintained at 85% because blood flow into and out of the CPB circuit is not constant and the oxygen carrying capacity is lower (hemodilution).

**Anticoagulation management**

The risk of intracranial hemorrhage was discussed earlier. Heparin dosing and cofactor activity differs in the premature. Higher doses per kg body weight may be required to achieve target-activated clotting time. We manage heparin therapy by monitoring heparin concentration (using heparin-protamine titration) and activated clotting times.

**Neuroprotection**

Strategies used for normal birth weight infants are adopted because of the paucity of data about neuroprotection during CPB for LBW infants. The prefer-

---

Table 4 Details of cardiac diagnosis and cardiopulmonary bypass (CPB) (n = 65)

<table>
<thead>
<tr>
<th>Diagnosis details</th>
<th>Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetralogy of Fallot, with/without pulmonary atresia</td>
<td>12 (18%)</td>
</tr>
<tr>
<td>Transposition of great arteries</td>
<td>10 (15%)</td>
</tr>
<tr>
<td>Truncus arteriosus</td>
<td>7 (11%)</td>
</tr>
<tr>
<td>Total anomalous pulmonary venous return</td>
<td>6 (9%)</td>
</tr>
<tr>
<td>Hypoplastic left heart variant (Sano-modified Norwood I)</td>
<td>6 (9%)</td>
</tr>
<tr>
<td>Ventricular septal defect and aortic arch obstruction</td>
<td>6 (9%)</td>
</tr>
<tr>
<td>Ventricular septal defect, with/without atrial septal defect</td>
<td>5 (8%)</td>
</tr>
<tr>
<td>Norwood aortic arch repair + Rastelli repair</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Pulmonary atresia with intact ventricular septum</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Tetralogy of Fallot, pulmonary atresia, aorto-pulmonary collaterals</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Partial or complete atrioventricular septal defect</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Hypoplastic left heart variant (Classic Norwood I)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Shone’s complex (repair of mitral valve, aortic valve, aortic arch)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Mitral valve repair + ventricular septal defect</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Aorto-pulmonary window + aortic arch reconstruction</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Single ventricle physiology</td>
<td>9 (14%)</td>
</tr>
</tbody>
</table>

**CPB details**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of CPB (min, median ± IQR)</td>
<td>142 ± 67</td>
</tr>
<tr>
<td>Duration of aortic cross clamping (min, median ± IQR)</td>
<td>67 ± 51</td>
</tr>
<tr>
<td>Deep hypothermic circulatory arrest (min, mean ± sd%)</td>
<td>30 ± 20/11</td>
</tr>
<tr>
<td>Selective antegrade cerebral perfusion (% of total)</td>
<td>16</td>
</tr>
<tr>
<td>pH stat acid-base management (% of total)</td>
<td>67</td>
</tr>
<tr>
<td>Aortic cannula sizes: 14G IV catheter/6 F/8 F (%)</td>
<td>4/1/85</td>
</tr>
<tr>
<td>Venous cannula sizes: 10 F/12 F/14F (%) of total</td>
<td>19/67/14</td>
</tr>
<tr>
<td>Circuit prime: packed red blood cells (ml, mean ± sd)</td>
<td>213 ± 34</td>
</tr>
<tr>
<td>Circuit prime: fresh frozen plasma (ml, mean ± sd)</td>
<td>60 ± 18</td>
</tr>
<tr>
<td>Circuit prime: crystalloid (ml, mean ± sd)</td>
<td>187 ± 82</td>
</tr>
<tr>
<td>Circuit prime: total volume (ml, mean ± sd)</td>
<td>393 ± 182</td>
</tr>
<tr>
<td>Phentolamine administered (%)</td>
<td>35</td>
</tr>
<tr>
<td>Methylprednisolone administered (%)</td>
<td>100</td>
</tr>
<tr>
<td>Minimum core temperature ($^\circ$C, mean ± sd)</td>
<td>22.3 ± 5.4</td>
</tr>
<tr>
<td>Minimum hematocrit on CPB (%, mean ± sd)</td>
<td>32 ± 5</td>
</tr>
<tr>
<td>Maximum hematocrit on CPB (%, mean ± sd)</td>
<td>45 ± 6</td>
</tr>
</tbody>
</table>

*Values expressed as percentage of total patients unless stated otherwise.
ence at Stanford is a hematocrit of 28–30% during CPB (103). We employ pH stat acid-base management if the induced hypothermia is severe enough (<26–28°C) to impair cerebral autoregulation (103). Elevated blood glucose concentrations are not treated intraoperatively and usually remain below 150 mg dl⁻¹. Safe limits for cerebral blood flow and cerebral perfusion pressure during CPB are unknown. This is particularly relevant during antegrade cerebral perfusion. Cerebral oxygenation monitoring by NIRS may be difficult because of the baby’s small forehead.

Patient size
The technical conduct of CPB is more challenging. CPB cannulae are small and can easily become displaced or obstructed. LBW patients seem more prone to electrolyte and pH abnormalities during CPB, perhaps because of the large circuit volumes. Administration of banked blood, cardioplegia, and saline can cause acidosis, hyperkalemia, and hypernatremia. Tro-methamine is a useful low-sodium buffer that is FDA approved for use during pediatric CPB.

Operating room preparation and patient transport
Standard protocol at Stanford includes: (i) scheduling nonurgent LBW cases during time of day when specialized hospital resources are readily available; (ii) preoperative collaboration between surgical, nursing, perfusion, and anesthesia staff to finalize intraoperative plan; (iii) priming the CPB circuit prior to transport of patient to operating room; (iv) use of neonatal ventilator; (v) if necessary, ability to deliver nitric oxide, nitrogen (to provide FiO₂ values in range of 0.16–0.21), or carbon dioxide to optimize pulmonary blood flow (59); (vi) operating room at suitable temperature and humidity and (vii) drug dilutions appropriate to patient weight.

Considerations for patient transport include: (i) appropriate equipment and medications for possible patient decompensation; (ii) use of gas blender to maintain pretransport FiO₂; (iii) measures to minimize heat and water loss from patient; (iv) full monitoring, including ETCO₂; (v) portable suction apparatus if endotracheal secretions are a concern; (vi) vigilance during hand ventilation to ensure Qp : Qs balance is maintained and (vii) confirm access to baby can be easily achieved when incubator is disconnected from power source.

Anesthetic technique
Appropriate anesthetic management for OHS requires an appreciation of the patient’s cardiac pathophysiology. LBW and term infants with the same type of cardiac lesion have similar cardiac pathophysiology and present the anesthesiologist with similar management challenges. However, there are some anesthetic issues that are especially relevant to LBW infants.

Anesthetic agents
The safety of general anesthesia for neonates and LBW babies in particular is currently under intense debate because anesthetic-induced neurotoxicity in immature animal models has been reported (108,109,118–122). Implicated drugs include N-methyl D-aspartate receptor antagonists (e.g., ketamine, nitrous oxide) and agents with GABA mimetic properties (e.g., diazepam, isoflurane, halothane, propofol). There are also data suggesting that these same anesthetics may be neuroprotective against hypoxic-ischemic injury and that inadequate analgesia during painful procedures may lead to increased neuronal cell death in animals and long-term behavioral changes in humans (119). Additionally, it is well recognized that inappropriate choice of anesthetic agent or dose can lead to suboptimal hemodynamics and cerebral hypoxia, thereby resulting in adverse neurological outcome. OHS in critically ill neonates and children has been associated with impaired developmental outcomes (104,123–125), but the contribution of anesthesia is unknown. The current Stanford approach is anesthesia induction with ketamine and rocuronium, maintenance with midazolam, low-dose isoflurane, and high-dose fentanyl (Table 5). A TIVA technique is mandated when an ICU ventilator is employed.

Monitoring
Optimally positioned umbilical artery and vein catheters are very useful for hemodynamic monitoring, drug administration, volume resuscitation, and blood sampling, but are not always in situ. Peripherally inserted central catheters are less practical because of their narrow lumen. We do not insert subclavian or internal jugular venous catheters because of concerns about trauma and thrombosis. Instead, two right atrial catheters are surgically inserted after sternotomy; one to monitor atrial pressure and the other for drug administration and volume resuscitation. When wrist arterial access is compromised, we prefer axillary artery (22G, 25-mm intravenous catheter) rather than femoral artery cannulation because of concerns about infection (proximity to perineum) and leg ischemia, although there are insufficient data to support this bias. Epicardial echocardiography is our standard for LBW infants although we do use intracardiac echocardiography catheters under a research protocol for patients >2 kg. Point of care laboratory tests facilitates ongoing assessment of the patient’s status. LBW infants are particularly prone to
hypo- and hyperglycemia during OHS, and frequent blood glucose monitoring is required.

Pulmonary

If the ETT has been in situ for > 5 days or if secretions are copious, we are usually inclined to change the ETT. We may upsize the ETT or replace it with a cuffed ETT if there is a substantial air-leak. This is done in anticipation of a CPB-induced lung dysfunction. After positioning the patient for surgery, a chest X-ray is obtained to verify satisfactory ETT placement. We attempt to maintain the preoperative mechanical ventilation and FiO2 goals, but not at the expense of hemodynamic stability or cerebral oxygenation. Accurate tidal volume delivery and ETCO2 monitoring at the ETT are required. These are best achieved with a sophisticated neonatal ventilator. An alternative for physicians who prefer an anesthetic machine ventilator would be additional respiratory monitoring with neonate-appropriate devices such as the NICO® monitor (Philips Respironics/Novametrix, Andover, MA, USA). Surfactant administration post-CPB has not been necessary to date.

Hemodynamic support

Milrinone, epinephrine, and dopamine infusions are typically used at Stanford. Ionized calcium values are maintained at the upper end of the age-appropriate range by infusing calcium chloride. Inhaled nitric oxide, typically ≤ 20 p.p.m. (126), is administered if PHT is suspected. Temporary epicardial pacing is employed for arrhythmias when indicated, but also when a sinus rhythm rate is relatively slow. When rewarming after CPB, target core temperature is limited to 35–36°C if there is concern about junctional ectopic tachycardia.

Hemostasis

The consequences of immature hemostatic function, cyanotic heart disease, liver dysfunction, hemodilution, inflammation, hypothermia, and surgical bleeding combine to greatly perturb coagulation. We do not use antifibrinolytic agents for LBW infants; the risks and benefits are unclear for this population. Fresh (<48 h) whole blood is not available at our institution. Activated Factor VII is only administered as rescue therapy. At Stanford, fresh frozen plasma is added to the CPB circuit during dilutional conventional ultrafiltration. Post-CPB, 1 unit (50 ml) of volume-reduced apheresed platelets and 2 units of cryoprecipitate are transfused to correct a predictable deficiency of platelets and fibrinogen (127). Further products are administered as necessary. All red cell units are washed to limit the hyperkalemia and acidosis associated with banked blood. Calcium chloride is infused (10–40 mg·kg⁻¹·h⁻¹) to mitigate citrate-induced hypocalcemia. All fluids are delivered via syringe pump to avoid inadvertent volume overload. Total volume of blood products transfused exceeds the patient’s estimated blood volume.

Other

Meticulous care is advised when padding and positioning the patient to minimize heat loss and skin trauma. The urinary catheter can be problematic; it is narrow and often obstructs or urine leaks around it.

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**Table 5 Anesthetic management (n = 65)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monitoring</td>
<td></td>
</tr>
<tr>
<td>Umbilical vein catheter (%)</td>
<td>32</td>
</tr>
<tr>
<td>Peripheral intravenous central catheter (PICC) (%)</td>
<td>21</td>
</tr>
<tr>
<td>Femoral venous catheter (%)</td>
<td>12</td>
</tr>
<tr>
<td>Internal jugular vein catheter (%)</td>
<td>2</td>
</tr>
<tr>
<td>Transthoracic right or common atrial catheter (%)</td>
<td>89</td>
</tr>
<tr>
<td>Transthoracic left atrial catheter (%)</td>
<td>46</td>
</tr>
<tr>
<td>Umbilical artery catheter (%)</td>
<td>37</td>
</tr>
<tr>
<td>Radial or ulnar or axillary artery catheter (%)</td>
<td>30</td>
</tr>
<tr>
<td>Femoral artery catheter (%)</td>
<td>33</td>
</tr>
<tr>
<td>Echocardiography:</td>
<td>89/11</td>
</tr>
<tr>
<td>epicardial/transesophagealb (%)</td>
<td></td>
</tr>
<tr>
<td>Ventilation</td>
<td></td>
</tr>
<tr>
<td>Cuffed ETT (%)</td>
<td>47</td>
</tr>
<tr>
<td>ETT sizes (mm) 2.5/3.0/3.5 (%)</td>
<td>0/28/71</td>
</tr>
<tr>
<td>FiO2 &lt; 0.21 at induction (%)</td>
<td>9</td>
</tr>
<tr>
<td>Intensive care ventilator:</td>
<td>25/2</td>
</tr>
<tr>
<td>conventional/oscillator (%)</td>
<td></td>
</tr>
<tr>
<td>Anesthetic technique</td>
<td></td>
</tr>
<tr>
<td>Anesthesia induction included ketamine (%)</td>
<td>79</td>
</tr>
<tr>
<td>Anesthesia maintenance included ketamine (%)</td>
<td>9</td>
</tr>
<tr>
<td>Anesthesia maintenance included isoflurane (%)</td>
<td>75</td>
</tr>
<tr>
<td>Isoflurane administered during CPB (%)</td>
<td>97</td>
</tr>
<tr>
<td>Midazolam administered (%)</td>
<td>77</td>
</tr>
<tr>
<td>Fentanyl administered (%)</td>
<td>100</td>
</tr>
<tr>
<td>Muscle relaxant: rocuronium/pancuronium (%)</td>
<td>83/17</td>
</tr>
<tr>
<td>Inotropes: dopamine/epinephrine/milrinone/calcium (%)</td>
<td>100/57/81/100</td>
</tr>
<tr>
<td>Furosemide administered (%)</td>
<td>63</td>
</tr>
<tr>
<td>Temporary pacemaker used (%)</td>
<td>35</td>
</tr>
<tr>
<td>Blood products administered intraoperatively</td>
<td></td>
</tr>
<tr>
<td>Packed red blood cells (units, median ± IQR)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Apheresed platelets (units, median ± IQR)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Fresh frozen plasma (units, median ± IQR)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Cryoprecipitate (units, median ± IQR)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Total blood products (units, median ± IQR)</td>
<td>7 (1.3)</td>
</tr>
</tbody>
</table>

CPB, cardiopulmonary bypass; ETT, endotracheal tube.

aValues expressed as percentage of total patients unless stated otherwise.

bStudy probe used, as per research protocol.

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Adverse intraoperative events

In the Stanford series, adverse events that affected anesthetic management occurred in 28% of surgeries (Table 6). Common problems were arrhythmia, pulmonary hemorrhage, decreased lung compliance after CPB, and excessive blood loss. Several patients desaturated during induction, suggesting marginal cardio-pulmonary reserve. In 48% of patients, the surgeon opted to not close the sternum and placed a silastic patch. Intraoperative extracorporeal membrane oxygenation (ECMO) support was never required. Similar reports for comparison were not found.

Outcome

Postoperative course

As indicated in Table 7, LBW patients typically have a prolonged recovery after OHS compared to term neonates (22,128). The most common morbidity identified in a recent study was infections of the bloodstream. Infections and chronic lung disease were associated with increased length of stay (22).

Mortality

LBW is a known risk factor for mortality following OHS with early mortality rates ranging from 10% to 42% (7,13–22,128–131). Interestingly, increased mortality and morbidity after OHS is recently reported for neonates delivered at 37–38 weeks gestation when compared to a control group of neonates born at 39–40 weeks gestation (128). Seventeen percent of the Stanford LBW patients died during postoperative hospitalization (Table 7). Mortality for two-ventricle repair (12%) was within the reported range for LBW infants (20,22,35). Mortality has been associated with high RACHS-1 and Aristotle preoperative risk assessment scores.

### Table 6

<table>
<thead>
<tr>
<th>Event</th>
<th>Weight (kg)*</th>
<th>In-hospital mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hemodynamic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension with chest closure</td>
<td>0.98</td>
<td>Died POD 1 from junctional arrhythmia and hypotension</td>
</tr>
<tr>
<td>Temporary ventricular dysfunction</td>
<td>2.4</td>
<td>Alive</td>
</tr>
<tr>
<td>(air in coronary)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventricular fibrillation during sternotomy</td>
<td>2</td>
<td>Died POD 37 from sepsis and multi-organ failure</td>
</tr>
<tr>
<td>Slow junctional arrhythmia</td>
<td>2.45</td>
<td>Alive</td>
</tr>
<tr>
<td>Junctional ectopic tachycardia</td>
<td>1.7</td>
<td>Alive</td>
</tr>
<tr>
<td>Junctional ectopic tachycardia</td>
<td>2.5</td>
<td>Died POD 67 from sepsis and multi-organ failure</td>
</tr>
<tr>
<td>Supraventricular tachycardia</td>
<td>1.1</td>
<td>Alive</td>
</tr>
<tr>
<td><strong>Respiratory</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brief hypoxia with induction</td>
<td>1.8</td>
<td>Alive</td>
</tr>
<tr>
<td>Hypoxia, bradycardia with induction; Pre-CPB hemorrhage in left upper lobe of lung</td>
<td>2.22</td>
<td>Alive</td>
</tr>
<tr>
<td>Difficult intubation: Failed direct and fiberoptic attempts, success using rigid bronchoscope</td>
<td>2.25</td>
<td>Alive</td>
</tr>
<tr>
<td>Significant airleak around ETT post-CPB; PHT</td>
<td>2.2</td>
<td>Alive</td>
</tr>
<tr>
<td>Blood in ETT causing occlusion</td>
<td>2.11</td>
<td>Alive</td>
</tr>
<tr>
<td>Blood in ETT causing occlusion</td>
<td>2.3</td>
<td>Alive</td>
</tr>
<tr>
<td>Blood in ETT causing occlusion</td>
<td>2.3</td>
<td>Alive</td>
</tr>
<tr>
<td>Hypoxia from inadequate pulmonary blood flow (Norwood stage I). Sano shunt revised.</td>
<td>2.42</td>
<td>Died POD 7 from bleeding following chest tube insertion</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PHT; liver hemorrhage</td>
<td>1.9</td>
<td>Died day of surgery from liver hemorrhage</td>
</tr>
<tr>
<td>Air conditioning problem after patient induced. Surgery delayed until issue resolved. Bleeding caused return to CPB</td>
<td>2.04</td>
<td>Alive</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

POD, postoperative day; CPB, cardiopulmonary bypass; ETT, endotracheal tube; PHT, pulmonary hypertension.

*Weight on day of surgery.
(13,132,133) and certain cardiac diagnoses (133). A meta-analysis demonstrated that first-stage reconstruction for hypoplastic left heart syndrome (HLHS) was a predictor of mortality in LBW infants (134), and mortality rates of 38% to 67% are reported (22,131,135,136). Hospital survival for Stanford infants who underwent this procedure (43%) was much lower than the institution’s reported survival (93%) for the overall HLHS population (137). LBW was also associated with increased mortality for infants undergoing the hybrid procedure for HLHS (138).

In the Stanford LBW series, patient weight was not predictive of outcome, and the mortality rate for very and extremely LBW babies (11%) was no worse than that for LBW infants (18%), suggesting it is reasonable to perform OHS on children weighing as little as 0.6 kg. Others have failed to find an association between very LBW (<1.5 kg) and mortality (7,18,19,22,131). It is likely that few infants in the lowest gestational age and lowest weights at birth had severe forms of congenital cardiac disease, as many of those infants do not survive to repair, or are not offered repair owing to extreme prematurity (22). SGA infants undergoing OHS have been reported to have increased risk for mortality and morbidity when compared to controls matched for gestational age (22), but several studies have found no association (131) or a suggestion of increased survival (17,22). Perhaps gestational age is a more important risk factor for poor outcome than weight (22). There is contradictory evidence on the influence of associated anomalies on mortality (7,17,20,22,130,131). The difference in reported outcomes could be related to the selection criteria for surgery. Postoperative factors that have been associated with mortality include cardiopulmonary resuscitation, ECMO, infection, and reoperation in the same admission (22,133,136).

The future

As these complex infants with multiple risk factors for adverse outcomes begin to have improved survival, the morbidity burden will be higher with a commensurate increase in length of stay and resource utilization. Perioperative care for LBW neonates with complex CHD frequently requires unplanned diagnostic and therapeutic interventions as well as multiple subspecialty consultations. This infrastructure may be most efficiently supported in high-volume centers in countries with sophisticated healthcare systems. The perioperative management described may not easily apply to populations and/or healthcare systems elsewhere (134,139).

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---

Table 7 Patient in-hospital outcome (n = 65)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital survivors</td>
<td></td>
</tr>
<tr>
<td>Total in-hospital survivors</td>
<td>54 (83%)</td>
</tr>
<tr>
<td>Postoperative mechanical ventilation (days, median ± IQR)</td>
<td>6 (8)</td>
</tr>
<tr>
<td>Duration in cardiac intensive care (days, median ± IQR)</td>
<td>10 (12)</td>
</tr>
<tr>
<td>Postoperative duration in hospital (days, median ± IQR)</td>
<td>20 (15)</td>
</tr>
<tr>
<td>Discharged to medical facility (% of total)</td>
<td>44</td>
</tr>
<tr>
<td>Nonsurvivors</td>
<td></td>
</tr>
<tr>
<td>Total in-hospital nonsurvivors</td>
<td>11 (17%)</td>
</tr>
<tr>
<td>Duration of ventilation (days, median ± IQR)</td>
<td>21 (28)</td>
</tr>
<tr>
<td>Duration in hospital* (days, median ± IQR)</td>
<td>22 (32)</td>
</tr>
</tbody>
</table>

*nAll nonsurvivors died during stay in Cardiovascular Intensive Care Unit.


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breaths at birth compromises the therapeu-
tic effect of subsequent surfactant replace-
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REVIEW ARTICLE

Total intravenous anesthesia (TIVA) in pediatric cardiac anesthesia

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Introduction

Total intravenous anesthesia (TIVA) (1,2) is useful for certain pediatric cardiac procedures and has become more feasible with improved infusion pump design, more appropriate pediatric software, and more clinical experience. There is a better understanding of the pharmacodynamics (PD) and pharmacokinetics (PK) of intravenous anesthetic agents in children undergoing cardiopulmonary bypass (CPB) and potential beneficial effects of these agents.

Pharmacodynamic effects of anesthetic agents during cardiac surgery

CPB may be associated with multiorgan damage, resulting in both immediate- and long-term effects (3,4). This damage may be related in part to inadequate regional tissue oxygen delivery and also to the ‘stress response’ during and after CPB (3). Reduction in the stress response to cardiac surgery in neonates and children is associated with improved postoperative outcome (3,5–9). Damage caused by inadequate oxygen delivery and tissue hypoxia may be reduced by metabolic depression using both hypothermia and anesthetic agents. These effects may be additive, for example, cerebral metabolic depression, in addition to that caused by hypothermia, may be produced with thiopentone or propofol or isoflurane titrated to EEG suppression during CPB (3,10). With thiopentone, this may result in reduced cerebral damage (3,11). However, to achieve EEG suppression, a large dose of thiopentone is usually required, which can produce hemodynamic instability, prolonged anesthetic effects, delayed tracheal extubation, and increased sedation during the first few postoperative days (11).

Cardiovascular effects of ketamine, propofol, and opioids

Ketamine

Ketamine is frequently chosen for anesthetic induction in patients with cyanotic conditions, as it increases systemic vascular resistance and cardiac output but without worsening right-to-left shunting (12). A recent prospective, randomized study by Tugrul et al. (13) demonstrated that ketamine anesthesia provided more stable precardio pulmonary bypass conditions than isoflurane anesthesia. Arterial oxygen tension, oxygen
satisfaction, and mean arterial pressure were better maintained poststernotomy in those patients receiving ketamine (13). Ketamine does not significantly increase the pulmonary vascular resistance in children with pulmonary hypertension (14).

Propofol
Propofol has a short half-life and context-sensitive half-time (CSHT), and when given by infusion with opioids, propofol can significantly attenuate the adverse hemodynamic and metabolic effects of bypass and surgery while producing rapid smooth recovery and transition to postoperative care (1). Propofol reduces whole body oxygen uptake during hypothermic CPB (28°C) in adults (3,15) and reduces cerebral perfusion pressure, oxidative stress, cerebral blood flow, velocity, and microembolic delivery. Propofol has also been shown to suppress seizures (3,16,17) and may act as an oxygen free radical scavenger (3,18). Propofol during CPB caused significant increases in mixed venous oxygen saturation, significant reductions in systemic oxygen uptake, reduction in glucose and cortisol concentrations with no difference in lactate concentrations, mean arterial pressure during CPB, and inotrope requirement after CPB, or in recovery times (3). Catecholamine and cortisol are released during stress, which produces alterations in microvascular permeability and multiorgan damage (3,19,20). These hormonal changes also result in hyperglycemia, which is known to worsen neurological outcome after cerebral ischemia (3).

During rewarming and normothermia, propofol can prevent hyperglycemia, attenuate the stress response, and produce rapid recovery (3). Propofol can be used in patients with or at risk of long QT syndrome without increasing the risk of torsades de pointes (TdP) (21).

Propofol produces arterial and venous dilation, both in systemic and in pulmonary circulation. These effects will be more prominent with the concomitant use of other vasodilators like alpha blockers, phosphodiesterase III inhibitors, and angiotensin-converting enzyme inhibitors. These circulatory effects can be modulated by optimizing the patient’s intravascular volume, surgical stimulation, propofol dose increments, and the rate of dose changes.

Opioids
Opioids do not cause myocardial depression and protect the heart by a preconditioning-like mechanism, and therefore, concurrent administration of opioids with either propofol or volatile agents produces an additive effect (22).

Preconditioning
Previous exposure of the brain and myocardium to minor insults, chemicals, or pharmacological agents can ‘precondition’ or increase the tolerance of neural and cardiac cells to lethal ischemic injury. Preconditioning with either volatile or intravenous agents may be advantageous. Some volatile agents, most notably isoflurane, when given before an ischemic insult have been found to induce ischemic tolerance in the brain and spinal cord (23–26) and to prevent ischemia/reperfusion (I/R) myocardial injury (27). There are several proposed mechanisms for protection (e.g., attenuating calcium overload, anti-inflammatory and antioxidant effects, pre- and postconditioning-like protection) (22). Anesthetic preconditioning with volatile anesthetics improves the recovery of contractile function and reduced calcium overload after I/R (28). Clarke et al. (29) showed recently that a critical factor mediating reperfusion injury of the heart is the mitochondrial permeability transition pore (MPTP). The opening of the MPTP causes mitochondrial swelling with release of proapoptotic proteins and uncoupling of mitochondrial oxidative phosphorylation. The resulting ATP deprivation causes the disruption of ionic homeostasis and contractile function and ultimately sarcolemma rupture and necrosis. Inhibition of MPTP opening during reperfusion protects hearts from reperfusion injury.

Propofol has been shown to protect the heart against cardiac insults in a variety of experimental models (30–32). These effects are attributed to its ability to act as a free radical scavenger (33), enhancing tissue antioxidant capacity (34), and through inhibition of plasma membrane calcium channels (35,36). Its antioxidant properties are responsible for its inhibitory action of MPTP opening in the Langendorff-perfused rat heart (30) and its antiapoptotic properties (36). The clinical benefits of propofol’s antioxidant capacity during CPB are more evident when using a high maintenance dose (plasma levels of approximate 4.2 ng·mL⁻¹) by Xia et al. (37). Propofol protects the myocardium against I/R injury, owing to its antioxidant effect and inhibition of the MPTP.

Cardiopulmonary bypass and pharmacokinetics of anesthetic agents
During CPB, a variety of factors act to alter drug disposition, metabolism, and elimination to a clinically significant extent. At the onset of CPB, the bypass circuit priming fluid is mixed with the patient’s blood. The volume of the prime and reservoir varies with age from around 350 ml in the neonate to 1500 ml in the
adult. This prime may be crystalloid or crystalloid mixed with albumin or blood. This mixture between patient’s blood and bypass circuit priming fluid will lead to a reduction in the patient’s packed red cell volume (PCV) to approximately 25%; plasma volume will be increased by 40–50%. All these changes may alter drug protein binding and distribution (38). This results in reduction in total drug concentration, although not always free drug. The potential changes in acid/base balance during CPB will result in changes in ionized and unionized drug concentrations, which affects protein binding. The ratio of the CPB circuit volume to the patients’ blood volume is greater for smaller patients than that for adults; consequently, this hemodilution effect and its effects on protein binding, volume of distribution, and drug clearance may be more pronounced in children as opposed to adults (39).

The mean arterial pressure is determined by the pump speed and the systemic vascular resistance which can be altered by the use of vasodilators and vasoconstrictors. Regional blood flow distribution and thus the drug distribution and metabolism can be varied. Hypothermia reduces hepatic and renal enzyme function, which affects drug metabolism. Many drugs bind to components of the CPB circuit (e.g., fentanyl) (39,40). There are important developmental influences on body composition (lipid, body water), body proportions, blood–brain barrier maturation, regional blood flow distribution, hepatic and renal functions which must be considered.

Propofol

Conflicting results have been obtained for propofol. The total concentration of propofol may decrease on commencing CPB with increase in the free fraction, or the total concentration may remain unchanged. A prolonged elimination half-life has been demonstrated in one study, but the redistribution half-life was short; concentration decreased rapidly after stopping the drug and patients made a rapid recovery. In general, the free active concentrations of these drugs remain unchanged but their action may be prolonged (38,41,42).

In a prospective trial of the accuracy of a pediatric target-controlled infusion (TCI) of propofol which employed the Paedfusor pharmacokinetic dataset (43), children did not show a significant change in PD effect (level of consciousness), because, even in small children, the volume of bypass circuit and reservoir is small in comparison with the volume of the central and other compartments. For example, in a child weighing 10 kg, the volume of prime would be 270 ml, whereas the volumes of the theoretical central, second, and third compartments would be 4600, 1340, and 8200 ml, respectively (43). Developments are underway to allow effect-site targeting in children (2).

Opioids

All opioids show a decrease in total drug concentration on commencing CPB. The degree of this decrease is greater with fentanyl where a significant proportion of the drug adheres to the surface of the CPB circuit (38). The decrease is least with opioids that have a high volume of distribution when the addition of the prime volume is less important and in those that can equilibrate rapidly to minimize the dilution effect (38). For alfentanil, fentanyl, and sufentanil (i.e. drugs that undergo hepatic biotransformation and elimination), CPB is associated with marked changes in PK properties. After CPB, the elimination half-life of fentanyl is prolonged, plasma clearance is decreased, and volume of distribution is increased (39,40). For alfentanil, CPB appears to prolong the elimination half-life and increase the volume of distribution, whereas clearance is unchanged (39,44). Free alfentanil concentrations remain relatively stable throughout CPB and pharmacologically active concentration remains unchanged (38). Remifentanil kinetics appears to be minimally affected by CPB with no change in the volume of distribution at steady state, the volume of the central compartment, or the elimination half-life (39). Target effect site concentration of remifentanil commonly used in TIVA varies. A target of 2–3 μg·l⁻¹ is adequate for laryngoscopy, 6–8 μg·l⁻¹ for laparotomy, and 10–12 μg·l⁻¹ for ablating the stress response associated with cardiac surgery (45).

CSHT is defined as the time taken for blood plasma concentration of a drug to decline by 50% after an infusion designed to maintain a state has stopped. CSHT is important when TIVA is used. Fentanyl has a short CSHT when given by infusion for a short time, but this dramatically increases as the duration of the infusion increases. Alfentanil’s CSHT becomes constant after 90-min infusion (Table 1). Remifentanil in contrast is context-insensitive with offset time independent of the duration of infusion because of its unique elimination by esterase cleavage.

<table>
<thead>
<tr>
<th>Table 1 Context-sensitive half-times (CSHT) of opioids in children [adopted from Mani and Morton (2).]</th>
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<td>Infusion duration (min)</td>
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<td>Sufentanil</td>
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Use of target-controlled infusion of propofol in children

TIVA in children has been reviewed in detail recently (2). TIVA can be delivered either by using a manual infusion scheme or by using a TCI. TCI uses a real-time PK model to calculate the bolus dose and infusion rates to achieve a user-defined target blood or effect site concentration. This is achieved by an infusion pump controlled by a microprocessor, which incorporates PK models with age-appropriate parameters. Comparative studies between TCI and manual infusion have shown better hemodynamic stability, lower induction dose, and faster recovery with TCI (46–49).

Pediatric pharmacokinetic models

There are several PK models for pediatric TCI devices, among them, with Paedfusor and Kataria datasets the most often used (50). TCI with propofol is limited to the age group of 3 years or more for most models (51). Recently, the Paedfusor has been modified to allow use down to 1 year of age and a lower weight limit of 5 kg. The Paedfusor is a prototype TCI system developed from a model concept developed by Schuttler whereby the clearance is adjusted for age. In children <12 years of age, clearance increases as age decreases (2). In the Paedfusor, the central compartment volume and clearance have a nonlinear correlation with weight and the size of the central compartment is quite larger compared with the Marsh pediatric (52) and Schuttler models. Thus, the user enters weight and age and the pump automatically enters the correct microconstants into the three-compartment PK algorithm. The accuracy of the Paedfusor system has been prospectively evaluated in 29 children aged from 1 to 15 scheduled for cardiac procedures (43,46,51); general anesthesia was provided using propofol administered by the Paedfusor system. Accuracy of the system was evaluated by obtaining up to nine arterial samples for the measurement of propofol concentration both during anesthesia and in the recovery period. The predictive indices of median performance error and median absolute performance error of the Paedfusor system were found to be much better than those found with the adult ‘Diprifusor’ system.

Potential problems with propofol

Propofol infusion syndrome is a metabolic disease usually associated with high dose (53–56) or long duration (55,57,58) of propofol and low carbohydrate intake. With the impairment of mitochondrial fatty acid oxidation, ATP production will be reduced and thus build up long-chain acyl-carnitine intermediates. Propofol infusion syndrome can manifest as unexplained severe metabolic, usually lactic acidosis, rhabdomyolysis, cardiac failure, renal failure, and usually of high mortality. In contrast to adults, higher target plasma and effect site concentration is needed for children to induce anesthesia and takes longer to reach the peak effect (2,59) and slower recovery from propofol infusion (2). This creates potential problems such as lipid overload and propofol infusion syndrome, especially after a long cardiac surgery. A healthy child requires 2–3 g kg⁻¹ day⁻¹ of lipid per day, equivalent to 4 mg kg⁻¹ h⁻¹ of 1% propofol in 10% soya oil. Lipid overload can be overcome by using 2% propofol solution, or by reducing soya oil to 5% from 10%, or by using propofol-sparing measures such as premedication, regional blockade, and/or concurrent use of systemic opioids; using TCI, monitoring depth of anesthesia, and tapering the infusion toward end of case, if possible, could allow more rapid recovery and may reduce such complications in children (2).

Propofol induces a drop in systemic vascular resistance, which may worsen the hemodynamics in patients with aortic stenosis, tetralogy of fallot, hypertrophic obstructive cardiomyopathy, balanced circulation, or right-to-left shunt.

Also, there are considerable gaps in PK models for some drugs for ill children and for young children, infants, and neonates, so caution is needed when applying such programs to these populations. Future models will incorporate more sophisticated PK/PD algorithms. Hence, when using the TCI technique at present, the anesthesiologist must still use knowledge and experience to titrate the intravenous agents to effect to avoid awareness, pain, and adverse effects (2).

Future of TIVA/TCI

The wide variability of PK parameters in the pediatric population compared with adults (46,60) suggests that the ability of a mathematical model to predict propofol cerebral effect is limited. This variability may be attenuated by using an open-loop TCI with clinical feedback input from EEG analysis, may play this role. Despite the lack of pediatric algorithm in the bispectral index (BIS) monitor, several studies have demonstrated a very good correlation between BIS values and measured or estimated propofol concentrations in children (59,61,62). Jeleazcov also reported that BIS can be used to monitor anesthetic effect produced by propofol in children above 1 year (63).

Currently, closed-loop TCI devices remain the preferred view of research laboratories and have not reached the...
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open market for use in humans. One major advance reported recently was the application of mass spectroscopy to measure propofol concentrations in the exhaled breath of adult and pediatric patients (64). There is a very good correlation between the exhaled and blood concentrations of propofol.

The importance of interindividual variability that characterizes the children population may be investigated using covariates as weight, age, and height to describe metabolic processes during physiological development in pediatric PK/PD modeling (46). Possible new formulations of propofol include emulsions that contain medium-chain rather than long-chain triglycerides (to possibly avoid propofol infusion syndrome), formulations with greater concentrations of propofol (2%), and water solution emulsions (microemulsions and phosphorylated propofol pro-drugs) (65).

Refinement of fast-tracking cardiac anesthesia techniques may be useful in the future. Experience with TIVA techniques in cardiac anesthesia is increasing. The next step is in making TCI equipment and pediatric software more widely available.

Clinical example of TIVA for pediatric cardiac anesthesia in the Royal Hospital for Sick Children, Glasgow

After preoperative assessment and patient preparation, we insert an intravenous cannula after EMLA cream application. Alternatively, we can perform inhalational induction with sevoflurane prior to iv catheter insertion. To reduce injection pain of 2% propofol, we preinject lignocaine 0.2 mg·kg⁻¹ and alfentanil 10–20 μg·kg⁻¹, wait for around 1 min, and then start a blood-targeted infusion of 2% propofol using an Alaris PK pump programmed with the Paedfusor dataset. An initial set blood target concentration of 2 μg·ml⁻¹ delivers a loading bolus dose of approximately 1 mg·kg⁻¹. We assess the patient’s response and titrate up the target concentration by increments of 1 μg·ml⁻¹ to achieve the desired induction conditions. Pancuronium is used for muscle relaxation as it counteracts any tendency of the induction agents to reduce heart rate. We taper our TCI target during vascular access.

Alfentanil will be titrated manually prior to sternotomy to a total of 50 μg·kg⁻¹ and then maintained with an infusion of 1–5 μg·kg⁻¹ min⁻¹; alfentanil is maintained during surgery and bypass with additional increments of 10 μg·kg⁻¹ prior to surgical stimulation, sternotomy, chest closure, drain insertion etc. The propofol target is maintained around 3 μg·ml⁻¹ during bypass. As propofol is a vasodilator, systemic vascular resistance is reduced and caution must be exercised during concomitant use of other vasodilators such as milrinone. Morphine and midazolam are typically given 30–60 min prior to discharge to the pediatric intensive care unit to assist transitioning to ongoing sedation and analgesia.

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REVIEW ARTICLE

Role of transesophageal echocardiography in the management of pediatric patients with congenital heart disease

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Introduction

Over the past two decades, transesophageal echocardiography (TEE) has solidified its role as a critical diagnostic and perioperative management tool for patients with congenital heart disease (CHD). TEE has proven to be invaluable in confirming preoperative diagnoses, formulating surgical plans, evaluating immediate operative results, identifying patients with residual defects, and guiding surgical revisions (1–8). Technological advancements, particularly the use of small probe sizes, have significantly improved patient safety and success of cardiac surgery in infants and children (9–20).

Transesophageal echocardiography has been shown to play an important role during cardiac catheterization procedures such as device placement, percutaneous valve replacement (21,22), and intracardiac ablations, as well as during noncardiac surgery in patients with CHD. Imaging through the transesophageal approach has been demonstrated to be of benefit in circumstances where other imaging modalities such as trans-thoracic echocardiography are not diagnostic (23).

This review highlights the use of TEE in the pediatric age group, focusing on indications, applications, complications, and contraindications of this imaging modality. A brief overview of TEE cross-sections and anatomical information derived from these is provided as relevant to the examination in CHD. Relevant information obtainable from intraoperative TEE in the pre and postbypass settings for selected congenital cardiac pathologies is described. Lastly, recent technological advances related to TEE in this patient population are noted.

Indications and applications of TEE in pediatric patients with CHD

Surgical applications

Surgical indications for TEE include both cardiac and noncardiac procedures.
Cardiac surgery
Intraoperative use is currently the most common indication of TEE in the pediatric age group. Numerous reports since the technology became available have documented the benefits of this approach, and the experience to date accounts for the incorporation of TEE into the standard of care of patients undergoing surgery for CHD at many centers worldwide.

Precardiopulmonary bypass
Transesophageal echocardiography is a beneficial diagnostic tool during the prebypass phase of surgery for CHD. TEE can corroborate preoperative diagnoses and define the anatomical abnormalities prior to the surgical intervention. In case of unsatisfactory trans-thoracic images or incomplete diagnostic data, TEE can help acquire the relevant missing information. Anesthesiologists can utilize TEE to assess ventricular preload, hemodynamic status, intracardiac/great artery shunting, and ventricular function, thereby guiding fluid management, anesthetic drug selection, and the use of inotropic/vasocative agents. Additional applica-

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**Figure 1** Mid-esophageal four-chamber view. All four cardiac chambers can be visualized in this view. Applications of this cross-section include the evaluation of chamber size and morphology, atrioventricular valve function, intracardiac shunting across the atrial and ventricular levels and ventricular function (global and segmental). RA, right atrium; TV, tricuspid valve; RV, right ventricle; LA, left atrium; MV, mitral valve; LV, left ventricle; IAS, interatrial septum; IVC, inter ventricular septum.

**Figure 2** Coronary sinus. Retroflexion of the probe at the level of the mid-esophageal four-chamber view displays the coronary sinus as it courses longitudinally along the atrioventricular groove to drain into the right atrium. An enlarged coronary sinus suggests the presence of a persistent left superior vena cava. RA, right atrium; RV, right ventricle; CS, coronary sinus; LV, left ventricle.

**Figure 3** Left pulmonary vein, spectral Doppler. View obtained by starting at the mid-esophageal four-chamber view, slightly withdrawing the probe and rotating to the left. Pulsed-wave Doppler interrogation of left lower pulmonary vein as it enters the left atrium. The spectral Doppler interrogation is guided by color flow mapping (red signal represents venous flow), as it drains normally into the left atrium. This examination is useful in the evaluation of pulmonary vein obstruction, diastolic dysfunction, mitral regurgitation, and atrial rhythm disturbances.

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Role of TEE in pediatric CHD patients
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tions of intraoperative prebypass TEE include confirmation of appropriate position of central venous catheters placed percutaneously (24,25).

**Bypass initiation**

Prior to initiation of cardiopulmonary bypass, TEE can confirm placement of venous cannulae and left ventricular venting device. During beating-heart surgery, TEE is helpful in assessing the presence of left-sided intracardiac air, allowing for recognition of...
potential systemic air embolization. TEE can be of benefit in eliminating the possibility of left ventricular dilation because of inadequate venting.

Figure 8 Mid-esophageal right ventricular inflow–outflow view. Cross-section obtained at 60° displays both atria, the inlet and outlet portions of the right ventricle, the aortic valve in short axis, the pulmonary valve and proximal main pulmonary artery. This view is essential in evaluating ventricular septal defects and defining their specific type. Perimembranous defects are seen in close proximity to the tricuspid valve (membranous region). In contrast, outlet (conal) ventricular septal defects are anatomically near the pulmonary valve. This view provides detailed information regarding the nature and severity of obstruction in lesions that involve the right ventricular outflow tract. In the figure, mild prominence of the conal septum is seen. RA, right atrium; LA, left atrium; TV, tricuspid valve; AV, aortic valve; RVOT, right ventricular outflow tract; RPA, right pulmonary artery.

Figure 9 Mid-esophageal two-chamber view. This cross-section displays the left atrium, left atrial appendage, anterior and posterior mitral valve leaflets, and left ventricle. The anterior and inferior walls of the left ventricle are well seen in this view and can be examined in the evaluation of segmental wall motion abnormalities. LA, left atrium; PMVL, posterior mitral valve leaflet; MV, mitral valve; LV, left ventricle; AMVL, anterior mitral valve leaflet; LAA, left atrial appendage.

Figure 10 Mid-esophageal aortic valve long axis view. This view is obtained at the level of the mid esophagus by rotating the scanning plane to approximately 120–140°. The view displays the left atrium, mitral valve, left ventricle, left ventricular outflow tract, aortic valve, and proximal ascending aorta. Portions of the interventricular septum and right ventricle are usually seen. Pathologies that may be characterized by this view include mitral and aortic valve disease, left ventricular outflow tract obstruction (discrete and tunnel-type), supravalvar aortic disease, and ventricular septal defects. In patients with hypertrophic cardiomyopathies, this view provides for characterization of septal thickness, anterior systolic motion of the mitral valve, mitral regurgitation, and the determination of outflow tract gradients. LA, left atrium; MV, mitral valve; AV, aortic valve; LVOT, left ventricular outflow tract; LV, left ventricle; RV, right ventricle; IVS, interventricular septum.

Figure 11 Transgastric mid short axis view. This cross-section is obtained by advancing the probe to the distal esophagus. Anteflexion is required to maintain adequate probe contact. This view provides for a quick assessment of ventricular filling, as well as global and segmental function. This mid papillary ventricular cross-section is particularly useful in determining the etiology of hypotension upon separation from cardiopulmonary bypass.
Postcardiopulmonary bypass

Transesophageal echocardiography has been shown to be of major benefit in assessing the adequacy of the surgical repair and in the detection of residual pathology such as outflow tract obstruction, shunting, valvular regurgitation, and stenosis. Such conditions can lead to difficulty in separation from bypass. In addition, TEE is used to facilitate cardiac de-airing and closely monitor ventricular function after the bypass period. This technology is also useful in the
assessment of hemodynamic status, thereby guiding fluid management and inotropic therapy (26–30). Postbypass TEE provides valuable information to the anesthesia and critical care teams in formulating postoperative management plans. The surgical placement of transthoracic lines may also be facilitated by the use of TEE.

Figure 16 Complete atrioventricular canal defect (Atrioventricular septal defect). The figure displays the anatomical defects associated with a complete canal defect. The defect in the inferior aspect of the interatrial septum is seen (primum atrial septal defect) just above the level of the common atrioventricular valve. A large inlet-type ventricular septal defect is also visualized. A, right atrium; LA, left atrium; LV, left ventricle; RV, right ventricle; VSD, ventricular septal defect; ASD, atrial septal defect.

Figure 17 Supravalvar aortic stenosis. Mid-esophageal aortic valve long axis view depicting narrowing just above the level of the sino-tubular junction in supravalvar aortic stenosis. This pathology characterized by a decreased in the caliber of the aorta above the valve level may be seen in patients with William syndrome. Evaluation by color Doppler typically demonstrates turbulent flow at the level of obstruction. AV, aortic valve.

Figure 18 Subaortic membrane. In this long axis view of the left ventricular outflow track, a discrete membranous ridge is seen attached to the ventricular septum below the aortic valve. In addition to assessing the gradient across the outflow tract, the examination should address aortic valve competence, as aortic regurgitation may be an associated finding. AV, aortic valve; RV, right ventricle.

Figure 19 Tetralogy of Fallot. Mid-esophageal long axis view in a patient with tetralogy of Fallot demonstrating the hallmark of this defect and anterosuperior deviation of the infundibular septum (left panel). This accounts for malalignment of the conal and trabecular portions of the ventricular septum and leads to crowding of the right ventricular outflow tract and associated obstruction. The aortic root is seen to override the ventricular septal defect. Color flow interrogation (right panel) is able to determine the magnitude and direction of shunting across the ventricular septal defect. LV, left ventricle; RV, right ventricle; IVS, interventricular septum; VSD, ventricular septal defect.

Noncardiac surgery
During noncardiac surgery, patients with CHD, acquired heart disease, heart failure, and pulmonary hypertension may present significant challenges to the anesthesiologist. TEE serves as a useful tool in the
clinical management of these patients. As in the case of cardiac surgery, TEE can assist the anesthesiologist to effectively optimize ventricular preload, afterload and contractility, and guide inotropic support and fluid management. In addition to the evaluation of global ventricular function, TEE is useful in the detection of wall motion abnormalities, thereby determining regional function and serving as a monitor for myocardial ischemia. Complications of operative procedures such as pericardial effusions can be detected by TEE and appropriate drainage if necessary instituted (31–41).

Transesophageal echocardiography during cardiac catheterization

Interventional procedures

The use of TEE has been documented during cardiac catheterization procedures that involve transcatheter
device closures of septal defects in the determination of exact position of the defect, size and relationship to surrounding structures such as atrioventricular valves, superior vena cava right pulmonary veins and aortic valve (21,22). Imaging via the transesophageal approach has been also shown to assist in positioning of wires, catheters, and devices (Clip S1), as well as in assessing residual shunting and encroachment of devices upon adjacent structures. Additional benefits include the evaluation of ventricular function and pericardial effusion/other procedure-related complications.

In patients with hypertrophic obstructive cardiomyopathy, TEE can precisely determine the site of injection during alcohol ablation. TEE can be used during balloon valvuloplasties or laser perforation of valvar atresia for monitoring, demonstrating immediate results of the procedures and to exclude any postprocedural complications.

**Catheter ablation**

In patients with supraventricular arrhythmias, TEE can be used to guide transeptal puncture and sheath placement into the left atrium for electrophysiologic mapping and ablation of left-sided pathways. This imaging approach can potentially prevent cardiac perforation. TEE facilitates positioning and manipulation of catheters used for radiofrequency ablation in normal and abnormal hearts, and serves as an adjunct to fluoroscopy (42–44).

**Other applications of transesophageal echocardiography**

**Ventricular assist devices**

After insertion of ventricular assist devices (VAD), the presence of an intracardiac communication can lead to potential right to left shunting causing hypoxemia. Valvar insufficiency and stenosis can compromise adequate device output and cause ventricular dysfunction based on pressure and volume overload. As these lesions can be addressed at the time of device insertion, TEE can play an important role in detecting these structural and functional abnormalities. Other useful applications of TEE include ensuring appropriate cannulae position and facilitating cardiac de-airing. TEE can assist in fine-tuning the settings for mechanical circulatory support and assessment of complications after VAD insertion such as pericardial tamponade and endocarditis (45). In the setting of biventricular dysfunction and placement of single support device, TEE is of significant benefit in determining if a second device (biventricular assist devices or biVAD) is necessary.

**Extra corporeal membrane oxygenation**

In patients undergoing extra corporeal membrane oxygenation (ECMO), the thorax may be covered by surgical dressings or the presence of an open sternum may preclude transthoracic imaging. In such cases, TEE may be used in the evaluation of ventricular function, cannula position and suitability for weaning of support. In the event of left atrial distension, TEE can determine the need for left atrial decompression and facilitate cannula positioning directly into the left atrium or stent placement across the interatrial septum if necessary (46).

**Diagnostic applications**

Diagnostic applications of TEE in patients with CHD include assessment of venous pathways in patients with transposition after baffle procedures, aortic root assessment in patients with repaired tetralogy of Fallot and other conditions associated with aortic root enlargement, and assessment of ventricular and valvar function in adult patients after Fontan surgery. In the case of endocarditis, TEE can precisely locate vegetation(s) or abscess and the resulting sequelae in affected areas. TEE can help determine the size, position and mobility of intracardiac tumors and monitor the effect of this on surrounding structures and physiological changes related to this.

In the postoperative or critical care setting, TEE may be able to provide diagnostic information that is not otherwise obtainable by the transthoracic echocardiography because of poor windows, dressings, or limitations related to patient size or body habitus. This is of particular benefit in adult patients with CHD. In such cases, TEE can be of benefit in the evaluation of cardiac tamponade, thrombus, ventricular function, volume status, and responsiveness to fluid (47–49).

**Complications related to transesophageal echocardiography**

Extensive experience has demonstrated that TEE can be safely performed in most pediatric patients with minimal complications. Complications related to probe insertion include failure to intubate the esophagus and vagal stimulation resulting in bradycardia. Although hemodynamic and respiratory complications occur rarely, it important to recognize that airway compromise by compression of airway structures may be seen in smaller patients. In neonates and small infants, the imaging probe can also result in hemodynamic alterations. Compression of the descending aorta as well as hypotension in neonates with total anomalous pulmonary venous return due to compression of posterior venous confluence by the probe has been reported.
Probe compression of anomalous vascular structures can also occur, as in the case of a retroesophageal subclavian artery, leading to alterations in the pressure monitoring tracing of the corresponding arm during probe manipulation.

Other problems such as dental trauma, jaw subluxation, mucosal erosion, and bleeding have been reported to occur rarely. Prolonged probe use can result in lip and tongue swelling. Unusual but more serious complications related to probe manipulation include deep mucosal lacerations or perforation of the esophagus or stomach.

Although the use of TEE in the young age groups is considered to be safe and complications occur rarely, the benefit-risk ratio should be examined in every case and physicians should be vigilant of the risks associated with this imaging modality and monitor patients accordingly (27,50–54).

Contraindications to transesophageal echocardiography in the pediatric patient

Contraindications to TEE in children as described by the Task Force of the Pediatric Council of the American Society of Echocardiography are noted in Table 1 (27). In the intraoperative setting during cases where esophageal instrumentation is not feasible, consideration may be given to epicardial imaging. Considerable experience over many years prior to the availability of suitable TEE probes in children provided evidence that this approach is safe and is of benefit in the intraoperative assessment of CHD.

The transesophageal examination in the patient with CHD

Guidelines have been established by the American Society of Echocardiography and Society of Cardiovascular Anesthesiologists for performance of a comprehensive intraoperative multipane examination (55). This consists of a series of 20 cross-sectional views of the heart and great vessels. Although these guidelines assume normal cardiac arrangement (cardiac mass in the left chest or levocardia, concordant atroventricular and ventricular connections), they serve as a reference point for the pediatric TEE examination. These views can be modified as necessary to obtain the pertinent information in most patients with structural heart disease, both children and adults.

A comprehensive TEE examination in children should include a systematic evaluation of all the cardiac chambers, valves, and vascular structures. The study should be systematic and organized so as not to miss any relevant information (55). In cases where the study needs to be limited or may need to be terminated prematurely because of ventilatory/hemodynamic instability or electrocautery interference, the examination should be focused and targeted to the relevant pathology if that can be anticipated.

A transthoracic echocardiographic examination in patients with CHD follows a segmental approach. This analysis involves defining the thoracoabdominal situs, cardiac position in the thorax, atrial situs, atrioventricular, and ventriculo-arterial connections. It also includes assessment of ventricular topology and relationship between the great arteries. Most of these anatomical details can be confirmed by TEE. The examination typically includes two-dimensional (2D) imaging, color flow interrogation, and spectral Doppler assessment. In some cases, additional modalities such as M-mode echocardiography may provide additional information. Contrast echocardiography using agitated saline or albumin injection into a peripheral or central vein may be particularly helpful in the determination of small intracardiac shunts, residual septal defects, and other vascular variants/pathology that may impact the perioperative management.

Anatomic information derived from selected TEE cross-sections is presented in Table 2 as a reference to evaluate normal and abnormal cardiovascular structures. Details of the pre- and postsurgical evaluation of specific congenital lesions are described in Table 3 (55–61).

Recent advances in transesophageal echocardiography

Two important advances in the field echocardiography with applications to pediatric and CHD include the development of the micromultiplane TEE probe and three-dimensional (3D) technology.
Table 2  Anatomical information obtainable from selected tee views

<table>
<thead>
<tr>
<th>Reference view</th>
<th>Multiplane angle (°)</th>
<th>Probe manipulation</th>
<th>Structures visualized</th>
</tr>
</thead>
<tbody>
<tr>
<td>ME 4 Ch</td>
<td>0–30</td>
<td>Neutral–slight retroflex</td>
<td>• Left and right atria&lt;br&gt;• Left and right ventricles&lt;br&gt;• Atrioventricular valves&lt;br&gt;• Segments of atrial and ventricular septum&lt;br&gt;• Three septal and three lateral left ventricular segments: basal (septal and lateral), mid (septal and lateral), and apical (septal and lateral) walls</td>
</tr>
<tr>
<td>Start at ME 4 Ch (Figure 2, Clip S3)</td>
<td>0–30</td>
<td>Retroflex</td>
<td>• Coronary sinus</td>
</tr>
<tr>
<td>Start at ME 4 Ch (Figure 3)</td>
<td>0–30</td>
<td>Anteflex/slightly withdraw probe and rotate to the left</td>
<td>• Left pulmonary veins</td>
</tr>
<tr>
<td>Start at ME 4 Ch (Figure 4, Clip S4)</td>
<td>0–30</td>
<td>Anteflex/slightly withdraw probe and rotate to the right</td>
<td>• Right pulmonary veins&lt;br&gt;• Superior vena cava&lt;br&gt;• Right atrial appendage</td>
</tr>
<tr>
<td>ME Asc Ao short axis (Figure 5)</td>
<td>30</td>
<td>Withdraw from ME 4 Ch and slightly anteflex</td>
<td>• Aorta&lt;br&gt;• Main pulmonary artery&lt;br&gt;• Origin of branched pulmonary arteries&lt;br&gt;• Aortic valve&lt;br&gt;• Coronary ostia&lt;br&gt;• Pulmonary valve&lt;br&gt;• Left and right atria&lt;br&gt;• Interventricular septum</td>
</tr>
<tr>
<td>ME Ao valve short axis (Figure 6, Clip S5)</td>
<td>30</td>
<td>Advance probe in neutral position from upper esophagus to display aortic valve in short axis. Withdraw probe to assess coronary origins and proximal course.</td>
<td>• Right and left atrium&lt;br&gt;• Tricuspid valve&lt;br&gt;• Right ventricular inflow&lt;br&gt;• Right ventricular outflow tract&lt;br&gt;• Pulmonary valve&lt;br&gt;• Proximal main pulmonary artery&lt;br&gt;• Left and right atria&lt;br&gt;• Interventricular septum&lt;br&gt;• Superior and inferior vena cava&lt;br&gt;• Left atrial appendage&lt;br&gt;• Coronary sinus&lt;br&gt;• Mitral valve&lt;br&gt;• Left ventricle&lt;br&gt;• Three anterior and three posterior left ventricular segments: basal (anterior, inferior), mid (anterior, inferior), and apical (anterior, inferior)</td>
</tr>
<tr>
<td>ME RV inflow–outflow (Figure 8, Clip S6)</td>
<td>60–80</td>
<td>Neutral</td>
<td>• Left atrium&lt;br&gt;• Mitral valve&lt;br&gt;• Left ventricle&lt;br&gt;• Two anteroseptal and two posterior left ventricular segments: basal (anteroseptal and posterior), and mid (anteroseptal and posterior) walls&lt;br&gt;• Left ventricular outflow tract&lt;br&gt;• Aortic valve and ascending aorta&lt;br&gt;• Left and right ventricles (short axis)&lt;br&gt;• Interventricular septum&lt;br&gt;• All six left ventricular segments at the mid level: mid (anteroseptal, anterior, lateral, septal, inferior, posterior)</td>
</tr>
<tr>
<td>ME bicaval (Figure 7, Clip S7)</td>
<td>90</td>
<td>Neutral</td>
<td>• Right atrium&lt;br&gt;• Interventricular septum&lt;br&gt;• Superior and inferior vena cava&lt;br&gt;• Left atrial appendage&lt;br&gt;• Coronary sinus&lt;br&gt;• Mitral valve&lt;br&gt;• Left ventricle&lt;br&gt;• Three anterior and three posterior left ventricular segments: basal (anterior, inferior), mid (anterior, inferior), and apical (anterior, inferior)</td>
</tr>
<tr>
<td>ME 2 Ch (Figure 9, Clip S8)</td>
<td>80–100</td>
<td>Neutral</td>
<td>• Left atrium&lt;br&gt;• Mitral valve&lt;br&gt;• Left ventricle&lt;br&gt;• Two anteroseptal and two posterior left ventricular segments: basal (anteroseptal and posterior), and mid (anteroseptal and posterior) walls&lt;br&gt;• Left ventricular outflow tract&lt;br&gt;• Aortic valve and ascending aorta&lt;br&gt;• Left and right ventricles (short axis)&lt;br&gt;• Interventricular septum&lt;br&gt;• All six left ventricular segments at the mid level: mid (anteroseptal, anterior, lateral, septal, inferior, posterior)</td>
</tr>
<tr>
<td>ME Ao valve long axis (Figure 10, Clip S9)</td>
<td>120–140</td>
<td>Neutral</td>
<td>• Coronary sinus&lt;br&gt;• Mitral valve&lt;br&gt;• Left ventricle&lt;br&gt;• Two anteroseptal and two posterior left ventricular segments: basal (anteroseptal and posterior), and mid (anteroseptal and posterior) walls&lt;br&gt;• Left ventricular outflow tract&lt;br&gt;• Aortic valve and ascending aorta&lt;br&gt;• Left and right ventricles (short axis)&lt;br&gt;• Interventricular septum&lt;br&gt;• All six left ventricular segments at the mid level: mid (anteroseptal, anterior, lateral, septal, inferior, posterior)</td>
</tr>
</tbody>
</table>

Role of TEE in pediatric CHD patients

K. Kamra et al.
Table 2  Continued

<table>
<thead>
<tr>
<th>Reference view</th>
<th>Multiplane angle (°)</th>
<th>Probe manipulation</th>
<th>Structures visualized</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deep TG long axis (left ventricular outflow tract view) (Figure 12, Clip S11)</td>
<td>0</td>
<td>Anteflex</td>
<td>• Left atrium</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Mitral valve</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Left and right ventricles</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Interventricular septum</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Left ventricular outflow tract</td>
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<td></td>
<td></td>
<td></td>
<td>• Aortic valve</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Proximal ascending aorta</td>
</tr>
<tr>
<td>Deep TG long axis (right ventricular outflow tract view)</td>
<td>0</td>
<td>Anteflex and rotate probe to the right</td>
<td>• Right ventricular outflow tract</td>
</tr>
<tr>
<td>Start at deep TG long axis (left ventricular outflow view) (Figure 13, Clip S12)</td>
<td></td>
<td></td>
<td>• Pulmonary valve</td>
</tr>
<tr>
<td>Start at deep TG long axis (complementary cross-section to deep TG long axis view at 0°)</td>
<td>90–120</td>
<td>Anteflex and rotate of probe to the left</td>
<td>• Proximal main pulmonary artery</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Superior vena cava</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Left ventricular outflow tract</td>
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<td></td>
<td></td>
<td></td>
<td>• Aortic valve</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Outlet ventricular septum</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Pulmonary veins</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Atrioventricular valves</td>
</tr>
</tbody>
</table>

Asc, ascending; Ao, aorta; Ch, chamber; ME, mid-esophageal; TG, transgastric.

Table 3  Intraoperative evaluation of congenital heart defects

<table>
<thead>
<tr>
<th>Congenital anomaly</th>
<th>Presurgical echocardiographic evaluation</th>
<th>Postsurgical echocardiographic evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial septal defect (Figure 14)</td>
<td>• Size</td>
<td>• Residual shunting</td>
</tr>
<tr>
<td></td>
<td>• Position</td>
<td>• Valve competence</td>
</tr>
<tr>
<td></td>
<td>• Magnitude and direction of shunt</td>
<td>• Interrogation of pulmonary and systemic veins to exclude obstruction</td>
</tr>
<tr>
<td></td>
<td>• Associated anomalies (e.g. PAPVR, cleft mitral valve, left SVC)</td>
<td>• Ventricular systolic function (applies to all defects)</td>
</tr>
<tr>
<td></td>
<td>• Mitral valve competence</td>
<td>• Monitoring of ventricular preload, air (applies to all defects)</td>
</tr>
<tr>
<td></td>
<td>• Right atrial and right ventricular size</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Baseline ventricular systolic function (applies to all defects)</td>
<td></td>
</tr>
<tr>
<td>Ventricular septal defect (Figures 8 and 15, Clip S13)</td>
<td>• Size, position and number of defects</td>
<td>• Evaluation or residual shunt(s) (2D, Doppler, and contrast echocardiography)</td>
</tr>
<tr>
<td></td>
<td>• Magnitude and direction of shunt</td>
<td>• AV and semilunar valve competence</td>
</tr>
<tr>
<td></td>
<td>• AV valve competence</td>
<td>• Estimation of systolic pulmonary artery pressure (TR/PR jets)</td>
</tr>
<tr>
<td></td>
<td>• Associated anomalies (e.g. tricuspid and aortic valve involvement)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Chamber enlargement</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Estimation of systolic pulmonary artery pressure (TR/PR jets)</td>
<td></td>
</tr>
<tr>
<td>Atroventricular septal defect (Figure 16, Clip S14)</td>
<td>• Morphology and distribution of atrioventricular valve tissue across ventricles</td>
<td>• Adequacy of the surgical repair (residual shunts, atrioventricular valve regurgitation or stenosis)</td>
</tr>
<tr>
<td></td>
<td>• Size and location of septal defects, and shunting (magnitude/direction)</td>
<td>• Estimation of systolic pulmonary artery pressure (TR/PR jets)</td>
</tr>
<tr>
<td></td>
<td>• Left AV valve cleft</td>
<td>• Left ventricular outflow tract (exclude obstruction)</td>
</tr>
<tr>
<td></td>
<td>• Regurgitation/stenosis across common atrioventricular valve</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Patency of outflow tracts</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Ventricular dimensions (balanced versus unbalanced)</td>
<td></td>
</tr>
<tr>
<td>Obstructive lesions involving the LVOT (Figures 17 and 18, Clips S15 and S16)</td>
<td>• Level (valvar, subvalvar, supravalvar)</td>
<td>• Residual obstruction</td>
</tr>
<tr>
<td></td>
<td>• Cause and severity of the obstruction</td>
<td>• Valve regurgitation (aortic and mitral)</td>
</tr>
<tr>
<td></td>
<td>• Morphology of LVOT/aortic valve/ascending aorta and measurements of involved/related structures</td>
<td>• Iatrogenic pathology resulting from the repair (e.g., ventricular septal defect and mitral regurgitation)</td>
</tr>
<tr>
<td></td>
<td>• Left ventricular size and wall thickness</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Aortic valve competence</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Associated defects</td>
<td></td>
</tr>
<tr>
<td>Congenital anomaly</td>
<td>Presurgical echocardiographic evaluation</td>
<td>Postsurgical echocardiographic evaluation</td>
</tr>
<tr>
<td>------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Obstructive lesions involving the RVOT</td>
<td>• Evaluation of right ventricular outflow tract for level and severity obstruction</td>
<td>• Residual obstruction</td>
</tr>
<tr>
<td>(Figures 19 and 20, Clip S17)</td>
<td>• Size of main and branch pulmonary arteries</td>
<td>• Valvar regurgitation (pulmonary and tricuspid)</td>
</tr>
<tr>
<td></td>
<td>• Evaluation of pulmonary and tricuspid valves for morphology, stenosis/regurgitation, and size of valve annuli</td>
<td>• Estimation of right ventricular/pulmonary artery systolic pressure</td>
</tr>
<tr>
<td></td>
<td>• Right ventricular size and wall thickness</td>
<td></td>
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<tr>
<td></td>
<td>• Associated defects</td>
<td></td>
</tr>
<tr>
<td>Transposition of the great arteries</td>
<td>• Confirmation of pathology by assessing segmental anatomy</td>
<td>• Residual defects (e.g., shunts, in atrial baffle operations evaluation of baffle leak and obstruction of venous pathways)</td>
</tr>
<tr>
<td>(Figure 21)</td>
<td>• Morphology, size and function of semilunar valves</td>
<td>• Evaluation of both semilunar valves for regurgitation and stenosis</td>
</tr>
<tr>
<td></td>
<td>• AV valve competence</td>
<td>• Outflow tract patency</td>
</tr>
<tr>
<td></td>
<td>• Outflow tract patency</td>
<td>• Biventricular function</td>
</tr>
<tr>
<td></td>
<td>• Origin and course of coronary arteries</td>
<td>• Left ventricular segmental wall motion abnormalities</td>
</tr>
<tr>
<td></td>
<td>• Presence of associated cardiac anomalies (e.g. septal defects)</td>
<td>• Truncal valvar regurgitation/stenosis</td>
</tr>
<tr>
<td></td>
<td>• Right atrial size</td>
<td>• Right ventricle to pulmonary artery reconstruction for stenosis or regurgitation</td>
</tr>
<tr>
<td></td>
<td>• Right ventricular size and function</td>
<td>• Residual defects</td>
</tr>
<tr>
<td></td>
<td>• RVOT/pulmonary valve patency</td>
<td>• Estimate of RV pressure</td>
</tr>
<tr>
<td></td>
<td>• Associated AV valve pathology</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Atrioventricular valve competence</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Coronary arteries</td>
<td></td>
</tr>
<tr>
<td>Truncus arteriosus</td>
<td>• Truncal valve morphology, stenosis, regurgitation</td>
<td></td>
</tr>
<tr>
<td>(Figure 22, Clip S18)</td>
<td>• Anatomy of the main and proximal branched pulmonary arteries</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Presence, position, size, and shunting across intracardiac defects</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Atrioventricular valve competence</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Coronary arteries</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Tricuspid valve function (regurgitation/stenosis)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Residual intracardiac shunting</td>
<td></td>
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<tr>
<td></td>
<td>• Residual RVOT obstruction</td>
<td></td>
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<tr>
<td></td>
<td>• Right ventricular systolic function</td>
<td></td>
</tr>
<tr>
<td>Single ventricle</td>
<td>• Morphology and displacement of tricuspid valve leaflets</td>
<td>Post-Norwood Procedure:</td>
</tr>
<tr>
<td>(Figure 23, Clip S19)</td>
<td>• Severity of tricuspid regurgitation</td>
<td>• Adequacy of interatrial communication</td>
</tr>
<tr>
<td></td>
<td>• Right atrial size</td>
<td>• AV and semilunar valve competence</td>
</tr>
<tr>
<td></td>
<td>• Right ventricular size and function</td>
<td>• Patency of systemic outflow</td>
</tr>
<tr>
<td></td>
<td>• RVOT/pulmonary valve patency</td>
<td>• Residual pathology if concomitant defect(s) addressed</td>
</tr>
<tr>
<td></td>
<td>• Associated AV valve pathology</td>
<td>Post-Glenn Operation:</td>
</tr>
<tr>
<td></td>
<td>• Atrioventricular valve competence</td>
<td>• Patency of cavopulmonary connection</td>
</tr>
<tr>
<td></td>
<td>• Atrial level shunts</td>
<td>• Antegrade flow across pulmonary valve (if pulsatile Glenn)</td>
</tr>
<tr>
<td></td>
<td>• Segmental anatomy</td>
<td></td>
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<tr>
<td></td>
<td>• Ventricular morphology</td>
<td>Post-Fontan/total cavopulmonary connection:</td>
</tr>
<tr>
<td></td>
<td>• Relationships between AV valves and ventricles.</td>
<td>• Inferior vena cava to pulmonary artery pathway to exclude obstruction</td>
</tr>
<tr>
<td></td>
<td>• Morphology and function of AV valves</td>
<td>• Assess for leaks if lateral tunnel Fontan completion</td>
</tr>
<tr>
<td></td>
<td>• Presence and adequacy of interatrial communication</td>
<td>• Flow across fenestration</td>
</tr>
<tr>
<td></td>
<td>• Outflow tract patency</td>
<td>• AV valve competence</td>
</tr>
<tr>
<td></td>
<td>• Associated defects</td>
<td>• Exclude pulmonary venous obstruction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Residual intracardiac defect</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Estimation of systolic right ventricular/pulmonary artery pressure</td>
</tr>
<tr>
<td>Anomalous pulmonary venous return</td>
<td>• Site of drainage and presence of obstruction across pulmonary venous pathways</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Atrial septum</td>
<td></td>
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<tr>
<td></td>
<td>• Associated cardiac defect(s)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Estimation of systolic right ventricular/pulmonary artery pressure</td>
<td></td>
</tr>
</tbody>
</table>

2D, two-dimensional; AV, atrioventricular; LVOT, left ventricular outflow tract; PAPVR, partial anomalous pulmonary venous return; PR, pulmonary regurgitation; RVOT, right ventricular outflow tract; SVC, superior vena cava; TR, tricuspid regurgitation.
Micromultiplane TEE probe

A miniaturized probe, referred to as a micromultiplane TEE device, has been recently developed to potentially increase the margin of safety of this imaging approach in neonates and the smallest infants (Figure 24). Initial experience have demonstrated that this probe can obtain good quality images in children weighing <3.5 kg without causing hemodynamic or ventilatory compromise (9,11,13,62,63).

Three-dimensional transesophageal technology

For patients over 30 kg in weight, the currently available 3D TEE matrix array probe can be used to enhance the morphologic, structural, and functional assessment. Particularly applications that may benefit from 3D imaging include the evaluation of valve pathology and percutaneous transcatheter interventions aimed at occlusion of septal defects (64–83). Recent data in adult patients with CHD already document the value of live 3D TEE imaging over conventional 2D scanning.

Supporting information

Additional Supporting Information may be found in the online version of this article:

- Clip S1 Transcatheter device closure of secundum atrial septal defect.
- Clip S2 Mitral stenosis.
- Clip S3 Coronary sinus.
- Clip S4 Right pulmonary veins, color flow Doppler.
- Clip S5 Mid-esophageal aortic valve short axis view.
- Clip S6 Mid-esophageal right ventricular inflow-outflow view.
- Clip S7 Mid-esophageal bicaval view.
- Clip S8 Mid-esophageal two-chamber view.
- Clip S9 Mid-esophageal aortic valve long axis view.
- Clip S10 Transgastric mid short axis view.
- Clip S11 Deep transgastric long axis view of the left ventricular outflow tract.
- Clip S12 Deep transgastric long axis view of the right ventricular outflow tract.
- Clip S13 Tetralogy of Fallot.
- Clip S14 Complete atroventricular canal defect (Atroventricular septal defect).
- Clip S15 Subaortic membrane.
- Clip S16 Supravalvar aortic stenosis.
- Clip S17 Tetralogy of Fallot.
- Clip S18 Ebstein’s anomaly of the tricuspid valve.
- Clip S19 Hypoplastic left heart syndrome.
- Data S1 Full legend for video clips.

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References

Role of TEE in pediatric CHD patients


Role of TEE in pediatric CHD patients


INTRODUCTION

Every year, approximately 10,000 children require anesthesia for congenital heart surgery during their first year of life (1,2). Advances in surgical techniques, cardiopulmonary bypass, anesthesia, and intensive care management have dramatically improved long-term survival in these children and have therefore focused attention on quality of life and neurocognitive outcomes (3–6). As the numbers of survivors increase and surgical procedures become more complex, there is a growing concern about the risk of abnormal neurologic outcome. The neurodevelopmental outcome of these children is quite variable: many are totally normal, while 20–50% of these children have neurologic impairment and developmental disabilities (7,8).

The etiology of neurologic impairment in these children has been studied and is multifactorial: brain immaturity (9–11), timing of surgery in cyanotic infants (12), prolonged low brain regional oxygen saturation (13), prolonged deep hypothermic circulatory arrest (14), and chromosomal anomalies (15). However, the effect of anesthetic exposure and neurologic outcome in these children is just beginning to be addressed (16,17). The potential detrimental effect of prolonged anesthetic exposure on the developing brain has recently become a public concern. Despite animal evidence supporting this concern (18–20), the clinical evidence in humans is limited to retrospective evaluations (21–23). More importantly, the effect of anesthetics on neurodevelopmental outcome in infants after repair for congenital heart disease needs to be further evaluated. The question to be answered, ‘Does the type of anesthetic used during surgical repair of congenital heart disease affect neurologic outcome?’ is complex. Thus, the aim of this article is to discuss the impact of chronic hypoxia, cardiopulmonary bypass, and anesthetics on the developing brain.

There are three factors to consider when assessing neurologic outcome in infants undergoing a prolonged anesthetic for surgical repair of congenital heart disease. Each of these factors will be discussed independently.

1. Chronic hypoxia: congenital heart disease, requiring surgical repair in infancy, is one usually causing hypoxia, such as transposition of the great vessels, truncus arteriosus, total anomalous pulmonary venous return, or hypoplastic left heart syndrome.

2. Cardiopulmonary bypass (ischemia/reperfusion injury): cardiopulmonary bypass is usually low-flow cardiopulmonary bypass; however, circulatory arrest is still used for some procedures at some institutions. More recent is the use of antegrade cerebral perfusion in some institutions. Regardless of the method of CPB, normal pulsatile blood flow to the brain is disrupted.

3. Prolonged anesthetic exposure: surgical repair for complex cyanotic heart lesions such as hypoplastic left heart syndrome, transposition of the great arteries, etc. requires a 4–6 h general anesthetic at most institutions.
Chronic hypoxia

The developing hypoxic brain may or may not be different than the developing normoxic brain. For example, using a perinatal rat model mimicking cyanotic heart disease, in which rat pups were maintained in a hypoxic environment (10% oxygen) for 1 and 4 weeks, there was no difference in neuronal cell death in the chronic hypoxia group as compared to those animals maintained in a normoxic environment for the same duration (24). Thus, a protective adaptive response may exist in the neonatal brain when exposed to chronic hypoxia (25,26).

This adaptive response to chronic hypoxia has been attributed to the N-methyl-D-aspartate (NMDA) 2B receptor subunit composition (27,28). The NR2B predominant subunit composition of the NMDA receptor early in life allows the fetus to tolerate hypoxic conditions in utero by avoiding excessive calcium influx via NMDA receptors (29–31) and thereby allowing the expression of brain-derived neurotrophic factor, which prevents apoptotic cell death (32,33). The NMDA receptor subunit composition switches to NMDA 2A with increasing developmental age, in response to increased PaO₂ after birth (30,31). Anesthetic agents, particularly, volatile agents act on the NMDA 2B receptor subunit composition (34). But how anesthetic agents affect the adaptive response to chronic hypoxia is not known.

Another adaptation to chronic hypoxia is cortical neurogenesis (35). It has been shown that 30% of cortical neurons are lost after chronic hypoxia and results in a reduction in brain volume. However, with the establishment of normoxia, in previously hypoxic brain, there is a 40% increase in cortical neurons but no increase in astrocyte or oligodendrocyte number. In normoxic brain, made acutely hypoxic, the re-establishment of normoxia increases the number of oligodendrocytes and astrocytes, but not neurons. Thus, with the establishment of normoxia in the developing chronic hypoxic brain, there is a loss of supporting structures, which may promote white matter injury. Furthermore, as to be discussed later, narcotic agents can influence neurogenesis.

Cardiopulmonary bypass

Cardiopulmonary bypass has been a great example of a global ischemic event followed by hypoxic reperfusion with resultant white matter injury. More recently, the use of antegrade cerebral perfusion has gained favor in some institutions. The impact of antegrade cerebral perfusion in long-term neurologic outcomes studies is currently being addressed (36). During circulatory arrest and possibly during low-flow cardiopulmonary bypass, cells in certain brain regions are known to die, whereas, other cells in the same region or different regions do not. This phenomenon, referred to as selective vulnerability, occurs in mature and immature brain (37–39). In neonates, neurons and, more importantly, oligodendrocytes in the neocortex and hippocampus are selectively vulnerable to death after deep hypothermic circulatory arrest. These events are felt to occur early, within hours of reperfusion and continue for several days postoperatively. The process of reperfusion during cardiopulmonary bypass, is that in which areas of the brain, formally deprived of oxygen, are now abundant in oxygen.

Overabundance of oxygen in the acutely hypoxic infant is a concern, and the use of hyperoxia, 100% oxygen, in the resuscitation of acutely asphyxiated infants is now being questioned (40–43). Evidence in neonatal human and animal models of acute hypoxia has determined that exposure to hyperoxia during and after a hypoxic period can generate excessive neurotoxic compounds. Markers of increased oxidative stress have been found in neonates as long as 28 days after resuscitation with 100% oxygen for acute hypoxia (44). Thus, the use of hyperoxia during cardiopulmonary bypass, a period of increased oxidative stress and inflammatory mediators (45), in normoxic neonates may not be as beneficial as previously thought. Furthermore, there are no studies that have evaluated the effects of cardiopulmonary bypass, with associated ischemia followed by hyperoxia, in a chronically hypoxic human or animal model in the presence or absence of anesthesia.

Prolonged anesthetic exposure

By nature of the surgical procedures being performed in these infants, anesthesia is required and the duration of exposure is several hours. A high-dose narcotic technique, as that used in the Boston Circulatory Arrest Trials, was a contribution of Anand and Hickey (46). Their clinical investigation in children undergoing anesthesia for surgical repair of congenital heart disease supported an improvement in overall outcome with the use of high-dose narcotics. High-dose narcotics reduced the stress response curve as determined by serum catecholamine and stress markers. The effect of stress, catecholamine binding to serotonergic and nicotinic receptors, and the amelioration of stress, binding of opioids to opioid receptors, can be influenced by development.
In general, binding of catecholamines to serotonergic and nicotinic receptors decreases dramatically as the developing human brain transitions between fetal, infant, and mature brain. Mature serotonergic receptor binding is about 25% of fetal binding and mature nicotinic binding is about 50% of fetal nicotinic binding (47), so the ability to mount a stress response decreases with increasing developmental age. Binding to opioid receptors remains relatively unchanged throughout brain development, but the opioid receptor subunit types do change (48,49).

Opioid receptors, specifically mu and kappa, are present early in gestation with delta receptors presenting later in gestation (50,51). The pattern of opioid receptor expression is cell type specific, and the action of a specific opioid receptor may be different based on the cell type: astrocytes, oligodendrocytes, and neurons. Fetal expression of the mu receptor is significantly decreased in the mature brain. The mu receptor is involved in regulation of neuronal and glial proliferation.

Opioid action on mu receptors in the developing brain inhibits neuronal and glial cell growth and division (52,53). During development, opioid action on kappa receptors promotes cell proliferation and offers neuroprotection. Thus, there is a developmental balance between mu and kappa receptors. Because of the influence of all three receptor subtypes (μ, κ, and δ) on astrocytes and oligodendrocytes, myelination is inhibited with the use of narcotics early in development (54). Concerns about preexisting white matter injury in infants prior to cardiopulmonary bypass, which may be exacerbated by chronic hypoxia and cardiopulmonary bypass, (55–57) may further question the use of narcotics before, during, and after these corrective surgical procedures.

As discussed previously with NMDA and opioid receptors, GABA_\text{A} receptor subunit composition changes during development as well (58,59). The transition in NMDA and GABA_\text{A} receptor subunit composition occurs around postnatal seven in a rat pup. A similar transition in the GABA_\text{A} receptor subunit composition occurs in humans as well (60). GABA_\text{A} receptors are pentameric structures containing predominantly z1 or z2 subunits in combination with β2 or β3 and a γ2 subunit. The GABA_\text{A} z and β subunits are crucial for the action of volatile anesthetics. The GABA_\text{A} receptor subunit composition transitions from being predominantly z2, early in development, to predominantly z1 later in development. The GABA_\text{A} z2 allows for early excitation via sodium–potassium-chloride transporter, NKCC1, which promotes synaptic growth and development, whereas GABA_\text{A} z1 allows for later inhibition via potassium-chloride transporter, KCC2 (61). Thus, loss of the GABA_\text{A} z2 composition or interaction with the GABA_\text{A} ligand-gated channel by GABA_\text{A}-specific agent such as sevoflurane or midazolam early in development may promote neuronal cell death.

Exposure to volatile anesthetics may cause morphological and functional responses in neural tissue that are dependent on the developmental stage of the tissue (62–65). This is likely attributable to developmental differences in GABA and NMDA receptor subunit composition. As a result, conclusions drawn from adult brain regarding responses to anesthetics (66–68) may be very different from responses of developing neural tissue in neonates and infants.

For example, Jevtovic-Todorovic et al. (18) exposed normal PND 7 rat pups to combinations of isoflurane, midazolam, and N_2O. Isoflurane caused neuronal apoptosis at the three concentrations studied; 1.5% isoflurane had the greatest effect on neuronal viability. Exposure of PND 7 pups to the combination of 1.5% isoflurane, midazolam, and N_2O caused neuronal apoptosis, necrosis, and learning and memory deficits measured months after anesthetic exposure. The effect in pups of other developmental stages was not evaluated.

Although this work has been criticized for lack of physiologic control during anesthetic exposure, it is consistent with other findings. NMDA antagonists (MK-801) initiate apoptosis in immature rat brain, the extent of which is dependent on both duration of exposure (4–6 h) and age (18,19). The effect on cell death increases as a function of postnatal age with maximal effect at PND7. However, it has been shown in preliminary work, from the same researchers, in animal models, that hypothermia, as used in cardiopulmonary bypass, can prevent the neurotoxic effects of anesthetics (69).

Contrary to the above work, volatile anesthetics have demonstrated neuroprotective effects in adult rat models of global and focal ischemia (70,71). Desflurane, a volatile anesthetic with properties similar to isoflurane in terms of cerebral autoregulation, confers neocortical and hippocampal neuroprotection in a piglet model of deep hypothermic circulatory arrest or low-flow cardiopulmonary bypass as opposed to a narcotic-based technique. This was confirmed with acute histologic examination and long-term neurologic evaluation. Neither the particular relevance of desflurane as compared to other volatile anesthetics nor has the effect of chronic hypoxia as opposed to normoxia been evaluated using a cardiopulmonary bypass model of developing brain.
In summary, there are limited in vivo, human or animal, investigations comparing the neuroprotective or neurotoxic effects of anesthetic agents in the developing cyanotic brain undergoing cardiopulmonary bypass in the absence or presence of surgical stimulus, let alone surgical repair for congenital heart disease. Conclusions drawn about anesthetic neurotoxicity in the developing normoxic brain could be potentially different than those drawn in the developing hypoxic brain. Furthermore, the effects of hyperoxia, as in cardiopulmonary bypass, in the developing hypoxic brain may need to be considered. Protective mechanisms developed in utero to tolerate chronic hypoxic conditions exist in the developing brain. Disruption of these mechanisms by anesthetic agents and high concentrations of oxygen and the subsequent effect on neurodevelopment is not known. Thus, at present, no conclusions can be drawn as to which is the best anesthetic agent or agents to use in these children.

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Anesthesia and congenital heart disease


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**Pediatric pacemakers and ICDs: how to optimize perioperative care**

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**Introduction**

As pacemaker and implantable cardioverter defibrillators (ICDs) become smaller, and surgical complexity increases, more pediatric patients are undergoing pacemaker and ICD therapy. This is reflected in the number of patients with these devices presenting for both cardiac and noncardiac surgery. Anesthesiologists caring for these patients need to have a sound understanding of the patient’s underlying heart disease and the intended device function, in addition to a practical algorithm for device optimization during the perioperative period.

This article reviews the nomenclature and basic function of permanent pacemakers and ICDs and indications for implantation in children and patients with congenital heart disease (CHD). A practical approach to the perioperative management of these devices is presented including potential complications and adverse events associated with them. Pacemakers and ICDs will be collectively referred to as cardiac rhythm management devices (CRMD).

**Pacemaker overview**

Permanent pacemaker systems consist of an impulse generator and leads. The leads may be attached to the endocardium via a transvenous approach or to the epicardium via a surgical approach. Transvenous systems are usually implanted via the left subclavian vein with the lead progressing into the right atrium and/or right ventricle. The pulse generator is then implanted in the left prepectoral region.

The decision for a surgical approach is dependent upon several factors, including age and size of patient as well as cardiac anatomy. Surgical placement of leads on the epimyocardial surface is usually via a minithoracotomy or subxiphoid approach, and the leads are then tunneled and connected to a pulse generator that is commonly implanted subcutaneously in the abdominal area.

Although the morbidity associated with epicardial lead placement is low (1), the leads are vulnerable to fracture and dislodgement (2) and are at risk of developing increasing pacing thresholds over...
time (3,4). Lead survival is superior in transvenous systems (2).

Regardless of the system used, it is generally believed that the greatest risk factor for damage to implanted leads is age at time of implant and the presence of CHD (2,5,6).

Children and infants have higher resting and peak heart rates than adults, which may increase battery utilization and significantly impact the longevity of pulse generators (5). In addition, limits to maximum tracking rates from some devices may result in a substantial decrease in exercise performance (7).

Pacemakers may be single chamber, dual chamber, or trichamber (resynchronization pacemakers) depending on patient size and indication for implantation. Leads are typically placed in the right atrium and/or right ventricle. In resynchronization systems, leads are usually placed in both the right and left ventricle. For endocardial systems, the LV lead is usually placed within the coronary sinus but atypical configurations have been described for patients with CHD. In patients with single ventricle physiology, a resynchronization system may signify two epicardial leads on a single ventricle.

Single chamber devices will sense intrinsic electrical activity from the corresponding chamber within a preset time limit. This will either inhibit or trigger pacing of that chamber depending on how the device is programmed.

Dual chamber devices can sense and pace both in the atrium and in the ventricle and maintain atrioventricular (AV) synchrony in patients without intact AV node function. AV synchrony is important in optimizing cardiac output by maintaining the atrial ‘kick’ which increases end diastolic volume resulting in increased stroke volume. AV synchrony can also lower atrial pressures (and hence congestive symptoms) as it eliminates ‘cannon’ a waves or atrial contraction against a closed AV valve.

Pacemakers sense intrinsic cardiac depolarization by measuring changes in the electrical potential of myocardial cells between the anode and cathode.

In unipolar leads, the pulse generator functions as the anode with the cathode located at the tip of the lead. Unipolar sensing produces a large potential difference because of the increased interelectrode distance. In bipolar systems, both the anode and cathode are situated on the lead with only a short distance between them. The advantage of the bipolar system is that less energy is required to produce a smaller potential difference. Electrical signals from outside the heart are less likely to be sensed, and thus, there will be a reduced susceptibility to electromagnetic interference (EMI). Recent years have seen a trend towards using bipolar leads.

The location and function of pacemakers are described using an internationally recognized code that was developed by The North American Society of Pacing and Electrophysiology (NAPSE) and the British Pacing and Electrophysiology group (Table 1) (8).

The five-position code shown in Table 1 is often shortened to the first three positions, e.g., single chamber pacemakers can pace the atrium (AAI) or the ventricle (VVI).

Dual chamber (DDD) mode is the most sophisticated and commonly used mode. Position IV describes rate modulation and is incorporated into most modern pacemakers. This function is commonly used in patients who do not have intact sinus node function, and it enables the pacemaker to automatically increase the heart rate to meet metabolic demands. Most patients with permanent pacemakers are programmed to the DDDR mode. The rate response can involve either atrial or ventricular pacing depending on the mode and underlying conduction abnormality. For instance, a patient with complete heart block and a single ventricular lead can have intact sinus node function but still require rate response in a VVIR mode. The most commonly used sensors are those that detect bodily accelerations because of motion (9). Sensors, which determine minute ventilation via changes in thoracic impedance, are also in use (9).

It is important to be aware of how rate modulation is accomplished, and as discussed later, it may be necessary to disable this function preoperatively.

Multisite pacing (position V) refers to the presence of more than one lead in a single cardiac

<table>
<thead>
<tr>
<th>I/chamber(s) paced</th>
<th>II/chambers sensed</th>
<th>III/response to sensing</th>
<th>IV/rate modulation</th>
<th>V/multisite pacing</th>
</tr>
</thead>
<tbody>
<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>T = Triggered</td>
<td>R = Rate modulation</td>
<td>A = Atrium</td>
</tr>
<tr>
<td>V = Ventricle</td>
<td>V = Ventricle</td>
<td>I = Inhibited</td>
<td>V = Ventricle</td>
<td>D = Dual</td>
</tr>
<tr>
<td>D = Dual</td>
<td>D = Dual</td>
<td>D = Dual</td>
<td>(T + I)</td>
<td>(A + V)</td>
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<tr>
<td>(A + V)</td>
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</table>

Table 1 Generic pacemaker code NAPSE/BPEG. Adapted from Ref. (8)
chamber or biventricular pacing. Biventricular pacing (also called cardiac resynchronization therapy) is an evolving technique of using simultaneous or near simultaneous pace activation of one or both ventricles to improve ventricular dysynchrony and cardiac function and is discussed later. Biaxial pacing is currently being investigated in clinical trials as a way to suppress atrial fibrillation but is not yet commercially available (9,10).

**Indications for permanent pacemaker implantation**

In 2008, the American College of Cardiology, American Heart Association, and Heart Rhythm Society updated the guidelines for pacemaker implantation and included recommendations for pediatrics and CHD (11). The main indications for pacing in children are sino-atrial (SA) node disease (including brady–tachy syndrome and symptomatic sinus bradycardia) and complete AV block (11).

An increasing number of pediatric patients are surviving palliative congenital heart surgery with impaired hemodynamics. Signs and symptoms that may not require pacing in an adult may have a significant impact on a child with borderline hemodynamics.

Sinus node dysfunction is not common in children with structurally normal hearts. It is more likely after certain types of palliation, e.g., late complication of tetralogy of fallot repair, after a Senning or Mustard procedure or total cavo-pulmonary connection (Fontan) for a single ventricle (12). The clinical significance of sinus bradycardia is age dependent, frequently asymptomatic, and rarely requires pacing. Current recommendations are displayed in Table 2.

Bradycardia–tachycardia syndrome, an arrhythmia where intra-atrial re-entrant rhythm alternates with severe bradycardia, is considered a Class IIa indication in patients following congenital heart surgery. This rhythm disturbance has been associated with significant morbidity and mortality in this population (13,14). Permanent pacing has been shown to prevent these episodes (15,16).

Third-degree AV block can be classified as either acquired or congenital in the pediatric population and is the most common indication for pacing in children. The commonest cause of acquired heart block in children is postoperative AV block and is usually a result of operations involving the interventricular septum around the area of the AV node. The current reported incidence stands at 1–3% (17,18). Patients with L-TGA or heterotaxy are also prone to developing complete AV block even without surgical intervention. A poor outcome has been described in patients with permanent postsurgical AV block who do not receive pacemaker therapy (19). Thus, pacing in the postoperative patient with AV block lasting more than 7 days is considered a Class I indication (11). Congenital complete AV block is usually associated with maternal lupus antibodies and presents as fetal or neonatal

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Indications for implantation of permanent pacemaker in children and adolescents. Adapted from Refs (5,11). Source: American Heart Association, Inc.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class I:</strong> Pacemaker implantation indicated</td>
<td></td>
</tr>
<tr>
<td>• Advanced second/third-degree AV block with symptomatic bradycardia, ventricular dysfunction, or low cardiac outputs or that persists at least 7 days postcardiac surgery</td>
<td></td>
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<tr>
<td>• Symptomatic age inappropriate sinus bradycardia</td>
<td></td>
</tr>
<tr>
<td>• Congenital third-degree AV block with wide QRS, complex ventricular ectopy, or ventricular dysfunction</td>
<td></td>
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<tr>
<td>• Congenital third-degree AV block in an infant with HR &lt;55 b/min or HR &lt;70 b/min in infant with CHD</td>
<td></td>
</tr>
<tr>
<td><strong>Class IIa:</strong> Pacemaker implantation reasonable</td>
<td></td>
</tr>
<tr>
<td>• Patients with CHD, sinus bradycardia, and intra-atrial reentry tachycardia</td>
<td></td>
</tr>
<tr>
<td>• Asymptomatic sinus bradycardia in child with complex CHD with resting HR &lt;40 b/min or pauses &gt;3 s</td>
<td></td>
</tr>
<tr>
<td>• Patient with CHD and impaired hemodynamics because of sinus bradycardia and loss of AV synchrony</td>
<td></td>
</tr>
<tr>
<td>• Unexplained syncope in repaired CHD patient complicated by transient AV block with residual fascicular block</td>
<td></td>
</tr>
<tr>
<td><strong>Class IIb:</strong> Pacemaker implantation may be considered</td>
<td></td>
</tr>
<tr>
<td>• Transient postop AV block that reverts to sinus rhythm with residual bifascicular block</td>
<td></td>
</tr>
<tr>
<td>• Congenital third-degree AV block in asymptomatic child/adolescent with acceptable rate, narrow QRS complex, and normal ventricular function</td>
<td></td>
</tr>
<tr>
<td>• Asymptomatic sinus bradycardia after biventricular repair of CHD with resting HR &lt;40 b/min or pauses &gt;3 s</td>
<td></td>
</tr>
<tr>
<td><strong>Class III:</strong> Pacemaker implantation not effective/contraindicated</td>
<td></td>
</tr>
<tr>
<td>• Transient postop AV block that reverts to normal AV conduction</td>
<td></td>
</tr>
<tr>
<td>• Asymptomatic Type I AV block</td>
<td></td>
</tr>
<tr>
<td>• Asymptomatic sinus bradycardia in adolescent with resting HR &gt;40 b/min and longest R–R interval &lt;3 s</td>
<td></td>
</tr>
<tr>
<td>• Asymptomatic postop bifascicular block in the absence of transient complete AV block</td>
<td></td>
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</tbody>
</table>

CHD, congenital heart disease; AV, atrioventricular.
bradycardia. This condition is associated with high postnatal mortality rates, and the bradycardia may result in a secondary dilated cardiomyopathy. Pacemaker implantation and normalization of heart rates are associated with a decrease in heart size and improvement in systolic function in these patients (20).

Cardiac resynchronization therapy is a way of improving mechanical efficacy and favors remodeling in hearts with ventricular dysynchrony. It aims to improve the timing and completeness of contraction in the right and left ventricle (for two ventricle patients) or to improve synchronized contraction within a single ventricle. There is emerging data, which indicates that long-term pacing of the right ventricle can cause secondary dilated cardiomyopathy and adverse remodeling of the left ventricle in some patients with congenital third degree AV block (21–23).

The most recent recommendation for resynchronization device implantation is adult guidelines (11) and include ejection fraction (EF) $\leq 35\%$, QRS $>0.12$ ms and New York Heart Association (NYHA) Class 3–4. Although there are no specific indications for children and CHD patients, resynchronization therapy has been used successfully in pediatric patients with poor function and electromechanical dysynchrony, who do not strictly meet the adult criteria. A retrospective multicenter study of 103 patients from 22 institutions published in 2005 (24) demonstrated the short-term efficacy of resynchronization therapy in pediatrics and CHD patients. This cohort experienced an improvement in the mean EF from 26% to 40%.

**Pediatric ICD overview**

Implantable cardioverter defibrillators have been in use for the past 20 years for primary and secondary prevention of sudden cardiac death. The ICD has all the capabilities of a pacemaker, with the additional potential for defibrillation of tachyarrhythmias (usually ventricular). It is also possible to program the defibrillator to pace terminate tachyarrhythmias such as monomorphic ventricular tachycardia.

Implantable cardioverter defibrillators are usually implanted transvenously using a lead that allows for sensing, pacing, and defibrillation. However, in small children and patients with CHD, it may not be possible to use the transvenous route. In that situation, novel configurations have been used, including placing the coil in the pericardial or subcutaneous space (25) (Figure 1).

Implantable cardioverter defibrillators measure each cardiac R–R interval, and when enough short R–R intervals are detected, an antitachycardia event is started. The device chooses antitachycardia pacing or shock depending on the presentation and programming. Most ICDs will also start pacing when the R–R interval is too long (antibradycardia function). All the tachycardia sensors in current use for ICDs are taken from the ECG.

About 20% of ICD patients have devices that incorporate sophisticated dual and biventricular pacing modes for permanent pacing (26).

Implantable cardioverter defibrillators also have an international generic code (Table 3). For complete identification, position IV is expanded into its full pacemaker code. For example, most devices with a rate responsive pacemaker and ICD will be identified as VVE-DDDR.

**Indications for ICD implantation in children**

Implantable cardioverter defibrillators are primarily implanted in patients who suffer a sudden cardiac arrest or those at high risk of malignant ventricular arrhythmias. The majority of patients with ICDs are adult patients with ischemic heart disease and poor EF. The published guidelines on the implantation of these devices in pediatrics are derived primarily from adult randomized clinical trials (11) (Table 4). In contrast to adults, there are currently no large prospective...
studies examining the efficacy of implantable defibrillators in children, and <1% of devices are implanted in the pediatric population. However, as technology advances, the use of ICDs in the pediatric and CHD population has expanded.

In 2008, Berul et al. (27) published the largest reported series of pediatric and congenital heart disease ICD patients. They conducted a retrospective review from four pediatric centers in the USA and collated information for all implants between 1992 and 2004. A total of 443 patients were included with a median age of 16 years. In 52% of patients, the ICD was implanted for primary prevention; 69% of patients had structural heart disease such as Tetralogy of Fallot (21%) and hypertrophic cardiomyopathy (14%). The remaining 31% of patients had structurally normal hearts with primary electrical diseases such as long QT syndrome, Brugada syndrome, and catecholamine-induced polymorphic ventricular tachycardia (VT). The authors reported that 26% of patients received appropriate shock therapy and 21% had inappropriate shocks. The main reasons for inappropriate shocks were lead failure (14%), sinus/atrial tachycardia (9%), and oversensing (4%).

This relatively high rate of inappropriate shocks is similar to that seen in other published pediatric series (28,29), and the authors concluded that higher inappropriate shock rates in children vs adults with CHD support the hypotheses that continued growth and activity place a strain on the ICD leads. In another study (29), growth was strongly associated with lead failure.

Thus, while ICDs in children may be life saving, there are a high number of inappropriate shocks and lead failures seen in this population. This should be

### Table 3

<table>
<thead>
<tr>
<th>Position I</th>
<th>Position II</th>
<th>Position III</th>
<th>Position IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shock chamber(s)</td>
<td>Antiarrhythmia pacing chamber(s)</td>
<td>Tachycardia detection</td>
<td>Antiarrhythmia pacing chamber(s)</td>
</tr>
<tr>
<td>O = None</td>
<td>O = None</td>
<td>E = Electrogram</td>
<td>O = None</td>
</tr>
<tr>
<td>A = Atrium</td>
<td>A = Atrium</td>
<td>R = Rate modulation</td>
<td>A = Atrium</td>
</tr>
<tr>
<td>V = Ventricle</td>
<td>V = Ventricle</td>
<td></td>
<td>V = Ventricle</td>
</tr>
<tr>
<td>D = Dual</td>
<td>D = Dual</td>
<td></td>
<td>D = Dual</td>
</tr>
<tr>
<td>(A + V)</td>
<td>(A + V)</td>
<td></td>
<td>(A + V)</td>
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</table>

### Table 4

<table>
<thead>
<tr>
<th>Class I: ICD implantation indicated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac arrest because of VF/VT and reversible cause excluded</td>
</tr>
<tr>
<td>Spontaneous sustained VT in CHD patients</td>
</tr>
<tr>
<td>Symptomatic sustained VT in CHD patients who have had EPS</td>
</tr>
<tr>
<td>Unexplained syncope in CHD patients with EPS inducible sustained, hemodynamically significant VT</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Class IIa: ICD implantation reasonable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent unexplained syncope in CHD patients with LV dysfunction or EPS-induced ventricular arrhythmias</td>
</tr>
<tr>
<td>Sustained VT with near normal ventricular function</td>
</tr>
<tr>
<td>Long QT or catecholamine-induced VT with recurrent syncope or VT despite B blockers</td>
</tr>
<tr>
<td>HCM or arrhythmogenic right ventricular dysplasia with one or more risk factors for sudden cardiac death</td>
</tr>
<tr>
<td>Brugada syndrome and syncope or VT that has not resulted in cardiac arrest</td>
</tr>
<tr>
<td>Nonhospitalized patients awaiting cardiac transplantation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Class IIb: ICD implantation may be considered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complex CHD patients with recurrent syncope and advanced ventricular dysfunction where thorough investigations failed to define cause</td>
</tr>
<tr>
<td>Long QT syndrome and risk factors for sudden cardiac death</td>
</tr>
<tr>
<td>Familial cardiomyopathy associated with sudden death</td>
</tr>
<tr>
<td>Patients with LV noncompaction</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Class III: ICD implantation not effective/contraindicated</th>
</tr>
</thead>
<tbody>
<tr>
<td>VT or VF from arrhythmias amenable to catheter ablation, e.g., WPW</td>
</tr>
<tr>
<td>Unexplained syncope with structurally normal heart and no inducible ventricular tachyarrhythmias</td>
</tr>
<tr>
<td>Ventricular tachyarrhythmias because of reversible cause in absence of CHD</td>
</tr>
<tr>
<td>Incessant VT/VF</td>
</tr>
<tr>
<td>Patients who do not have reasonable expectation of survival/functional status of 1 year</td>
</tr>
</tbody>
</table>

ICD, implantable cardioverter defibrillator; CHD, congenital heart disease; EPS, electrophysiology study.
kept in mind when managing these patients during the perioperative period.

**Preoperative assessment and preparation**

Adequate preoperative assessment and preparation are essential in the pediatric patient with a CRMD.

The ASA practice advisory for the perioperative management of patients with a CRMD recommends that the patient should have a preop evaluation focusing on three main areas (30):

1. Type of device
2. Dependency on device for antibradycardia pacing and underlying escape rhythm
3. Device function

Several investigators have shown that an incomplete preoperative evaluation may lead to adverse outcomes (31–33). An observational study of 60 adult patients scheduled for noncardiac surgery showed that preoperative interrogation detected pacemaker dysfunction in 12% of patients (34), thus highlighting the importance of a preoperative evaluation.

In adults, battery malfunction is the most common cause of generator device failure with ICD malfunction rate substantially higher than pacemakers (35).

Children are considered to have a higher risk for lead failure and fracture than adults. Lead failure remains the most common cause of inappropriate shocks and ICD complications in children (27).

The preoperative assessment should include a focused history and examination to determine the indication for CRMD, coexisting cardiovascular pathology, pocket generator location, and any cardiac conditions that may influence defibrillator pad position, e.g., Dextrocardia.

Ideally, patients will have a device information card containing the make, model, and serial number of the device. Patient medical records or old operative notes may also have this important information and may contain the most recent interrogation report.

A patient history of symptomatic bradycardia or syncope or successful AV nodal ablation prior to device implantation may indicate pacemaker dependency. A chest x-ray (CXR) can help in determining the type of device (ICD vs pacemaker) and whether it is single, dual, or biventricular (Figures 1 and 2). It can also be used to determine the number, position, and integrity of leads as well as any unusual configurations of lead/generator placement and tunneling that may impact the surgical approach.

A recent 12-lead surface ECG should also be obtained to determine whether the pacemaker is being used and which chamber is being sensed and/or paced.

Ultimately, the only reliable method of assessing battery status, lead placement, and adequacy of pacemaker/ICD settings is direct interrogation with a programmer. This is usually performed by dedicated electrophysiology staff, cardiologist, or an industry representative. Pacemakers should be routinely interrogated once a year and ICDs every 3–4 months (9,26). It is recommended that all devices with ICD function should be assessed within 30 days of surgery (36) but there is no agreed consensus on acceptable timing for those with only pacemaker function. A copy of the most recent interrogation report should be obtained, which should include the patient’s underlying rate and rhythm and the need for intraoperative back up pacing support. It may also contain information on whether a magnet mode is present and the preset magnet response of the device.

For elective surgery, it is always prudent to discuss the case in advance with a cardiologist or qualified programmer informing them of the surgery date, type, and sources of EMI so that they have adequate time for device optimization.

Figure 3 summarizes a practice algorithm that may be used for optimization of devices during the perioperative period. Occasionally emergency surgery will preclude a full interrogation of the device. In those situations, it is still important to use as many of the strategies depicted as possible depending on the time constraints of the emergency procedure.
Electromagnetic interference and reprogramming

Safe perioperative management of pacemakers is dependent on understanding and effectively managing EMI in the operating room.

Electromagnetic interference, radio-frequency waves in the 50–60 Hz range, can be generated in the perioperative setting in a multitude of ways. Electrocautery, transthoracic defibrillation, therapeutic radiation, radio-frequency ablation, extracorporeal shock wave lithotripsy, MRI, nerve stimulators, fasciculations, shivering, and large tidal volumes have all been shown to cause EMI (9,30).

Electromagnetic interference can cause either inappropriate triggering or inhibition of paced output as well as reversion to an asynchronous (noise suppression) mode (9). Asynchronous pacing may compete with a spontaneous rhythm and lead to an arrhythmia. For ICDs, inappropriate triggering may lead to inappropriate shock or antitachycardia therapy.

There is also a risk that a current can be induced in the leads resulting in electrical discharge to the myocardium, which may produce arrhythmias or even a burn.

Modern devices are less susceptible to EMI because of the use of bipolar leads, improved filters and circuit shields, which insulate the internal electronics from the metal casing device, and improved noise protection algorithms, which filter signals out with the range of normal cardiac noise. However, the risk of EMI interference still exists even with modern, sophisticated devices.

The ASA task force recommends reprogramming to an asynchronous paced mode in patients who are pacemaker dependent when there is a significant risk of EMI (30). Reprogramming to an asynchronous mode at a rate higher than the patients’ intrinsic rate will overcome potential oversensing or undersensing from EMI. If possible, qualified personnel should be contacted before the procedure to allow time for optimal

Figure 3 Practice algorithm for perioperative management of cardiac rhythm management device (CRMD).
device management. Reprogramming should be performed prior to skin preparation and draping of the patient so that access to the device is not hindered. In emergency situations, where time may preclude reprogramming by qualified personnel, a magnet may be placed over the device to revert to asynchronous pacing. Occasionally switching to asynchronous pacing may cause hemodynamic disturbances; therefore, it is important to have all the patient monitors in place before changing modes.

Special algorithms such as rate adaptive functions should be disabled (30).

It is also recommended that the ICD antitachyarrhythmia function should be disabled (30) and a qualified programmer should do this. Although a magnet should not be used routinely to disable ICDs (30), it can be used in an emergency situation. Patients with disabled ICDs should have transthoracic defibrillator pads in place.

Reprogramming a device will not protect it from damage or reset caused by EMI. Between 1984 and 1997, the US FDA was notified of 456 adverse events related to diathermy (26).

Adequate monitoring remains vital, and it is prudent to reduce EMI as much as possible. This includes use of bipolar diathermy or ultrasonic scalpel especially if surgery is within 15 cm of the generator. If monopolar diathermy must be used, then cutting (minimal power setting) rather than coagulation current and short intermittent irregular bursts <1 s duration should be used (37).

Good skin contact with the diathermy grounding pad should be ensured, and it should be placed far away from the device, in a way that current flow will not intersect the pacing system (26). For example, for head and neck surgery, the grounding pad should be placed on the shoulder contralateral to the device and not on the thigh.

**Magnet use**

The appropriate role of magnets in the perioperative period remains controversial. Magnet activated switches were incorporated into pacemakers to demonstrate remaining battery life and sometimes pacing threshold safety factors (26). They are not specifically designed to treat pacemaker emergencies or to treat EMI effects. Placing a magnet over the center of the pacemaker will usually cause it to revert to an asynchronous pacing mode (AOO, VOO, or DOO) where no intrinsic cardiac activity is sensed. The pacemaker will pace at a preset ‘magnet rate’ which will vary according to the device manufacturer and model. For example, Medtronic magnet rate is usually 85 b·min⁻¹, whereas the St Jude rate is usually 100. It is important to appreciate that a preset magnet rate may not be sufficient to meet the metabolic demands of a pediatric patient. The preset magnet rate may also vary according to the battery voltage (i.e., life) of the generator, e.g., for Boston Scientific devices, the preset magnet rate is usually 100 b·min⁻¹ but may decrease to 80 when there is only 3 months left on the battery life. Magnet placement on a device at the end of service life can cause cessation of pacing altogether.

Although most ICDs will suspend antitachycardia therapy when a magnet is placed over the device, like pacemakers, magnet response varies according to the manufacture and device program. There are also differences between manufacturers with regard to where to position the magnet (36).

Only an interrogation with a programmer can reveal current magnet response settings. When a magnet is used for CRMDs with combined pacemaker/ICD function, the ICD function will be suspended but the device will not be forced to revert to an asynchronous pacing model. Patients with these devices who are pacemaker dependent need to have their device reprogrammed to an asynchronous mode preoperatively if there is significant risk of EMI such as diathermy.

In general, details about magnet response can be obtained from the manufacturer’s helpline. It is important before starting a procedure for a patient with a CRMD to know where the nearest magnet is situated and to locate the patient’s generator position in case it needs to be accessed in an emergency.

**Intraoperative management**

It is essential that ECG monitoring of the patient includes the ability to continuously detect pacemaker activity. A perfused peripheral pulse should be monitored with a waveform display, e.g., pulse oximetry or invasive pressure monitoring. Other modalities that confirm pulse generation during pacing include manual palpation and auscultation via a precordial or esophageal stethoscope. One should have a low threshold for beat to beat arterial pressure monitoring especially for long procedures with significant fluid shifts and in patients with resynchronization devices, heart failure, or hypertrophic cardiomyopathy. Temporary pacing and defibrillation equipment should be immediately available before, during, and after the procedure.

It is recommended that transthoracic defibrillator pads should be placed in an anterior–posterior position and as far away from the pulse generator as possible.
Transthoracic defibrillation may result in reprogramming of the pulse generator, damage to the device circuits or myocardial burns. If an external defibrillator has been used during a procedure, it is essential to interrogate the device postop to assess for any damage.

Although the ASA task force believes that anesthetic techniques do not influence CRMD function (30), it is important to pay attention to choice of anesthetics in patients with CRMD devices. Drugs that suppress the AV or SA node (e.g., dexamethasone, potent opiates) may render the patient pacer dependent. Inhalation agents such as Isoflurane or Sevoflurane may exacerbate long QT syndrome and cause arrhythmias.

Three main reasons for pacemaker failure are failure to capture, lead failure, and generator failure. The last two are rare in a system that has been adequately interrogated preop. If lead failure does occur in a patient who is pacemaker dependent, alternative methods of pacing include external transcutaneous pacing and temporary transvenous pacing.

Pacemakers may exhibit acutely elevated lead thresholds and failure to capture with metabolic perturbation or ischemia (26,38). Electrolyte and metabolic abnormalities, especially hyperkalemia, metabolic acidosis and alkalosis, hypothermia, and hyperglycemia all significantly increase the pacing threshold (38). Therefore, large fluid shifts, dehydration, and significant bleeding during the perioperative period may in turn influence pacemaker function. Hypoxemia and hypercarbia have also been shown to independently increase the myocardial stimulation threshold (38).

Postoperative care

Any pacemaker that was reprogrammed for the surgery should be reset at the end of the procedure. Most manufacturers advise re-interrogation of all devices postop especially if monopolar diathermy, significant fluid or blood component administration, or external defibrillation have been used (30). Pacing and sensing thresholds should be measured, and the device should be programmed to optimize hemodynamics in the postoperative setting. Pediatric patients with DDD pacing who develop sinus tachycardia may reach their Wenckebach or 2:1 block point, so it is helpful to know what these are for each patient and try to avoid extreme sinus tachycardia. ICD patients should be monitored until the antitachycardia therapy is restored.

Conclusion

Pediatric patients with permanent pacemakers and ICDs present unique management challenges during both cardiac and noncardiac surgery. It is critical for the anesthesiologist caring for these patients to be adept at assessing and managing patients with these devices in the perioperative period.

References

Pediatric pacemakers and ICDs


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Introduction

Cerebral oximetry with near-infrared spectroscopy (NIRS) is a noninvasive, continuous assessment of brain oxygen delivery and utilization (1). NIRS-based cerebral oximeters quantitate a venous-weighted ratio of oxygenated and deoxygenated hemoglobin in the region of cerebral cortex underlying the sensors, usually placed on the forehead. Initially hailed as the ideal neonatal neuromonitor, currently marketed cerebral oximeters have gained more traction in the operating room functioning more as hemodynamic monitors, where they are practically suited for use during cardiopulmonary bypass. There is no standard of care for the use of NIRS-based cerebral oximetry in Pediatric Anesthesia, although it has its greatest presence in pediatric cardiac anesthesia. Proponents of NIRS-monitoring cite validation data, physiologic principles, and common sense (2), while opponents of the use of NIRS cite a lack of rigorously demonstrated outcome improvement and cost (3). Evidence-based medicine distinguishes medicine as a science from mysticism. However, if strict evidence is required for every aspect of care of the critically ill child, providers will have no room to maneuver effectively. While the academic intransigent appears to lack common sense, common sense can also be misleading, harm patients, and drive up medical costs (4,5). Considering that none of the monitors currently used in the operating room have been shown to improve long-term outcome, how can the operative team evaluate the cost/benefit ratio of cerebral oximetry monitoring?

There may not be an accessible way to delineate the value or harm of a monitoring device, as precedent attempts with other monitors have failed to do so (6,7). Therapeutic interventions for critically ill children are often performed with imperfect evidentiary data, commonly extrapolated from adult studies, or absent entirely (8). Given the latitude of clinical practice resulting from data paucity, it is the responsibility of the pediatric intensivist and anesthesiologist to be familiar with the data that are available. We will provide a focused overview of NIRS technology, a brief review of specific validation data for NIRS use, clinical outcome data relevant to pediatric practice, and a proposed clinical treatment algorithm for desaturation.
events detected with NIRS. We will discuss the changes in practice that have occurred temporally with the use of NIRS monitoring.

**Reflectance NIRS**

Frans Jobsis first described the measurement of cerebral oxyhemoglobin content using reflectance NIRS in 1977 (9). Near-infrared light with a wavelength between 650 and 950 nm penetrates biologic tissue without harmful ionization and is absorbed by a limited number of chromophores found in human tissue – notably hemoglobin (Hb), oxyhemoglobin (Hb-O2), and cytochrome aa3. Further, these chromophore species absorb light differentially across the near-infrared bandwidth, so the use of multiple wavelengths of light permits quantitation of the relative concentrations of Hb and Hb-O2 separately. Cytochrome aa3 is the last enzyme in the mitochondrial oxygen transport chain, so there has been interest in measuring the redox-state of this molecule as a marker of cellular oxygen availability, but this technique has been limited to investigational work.

Although the marketed cerebral oximeters and pulse oximeters use proprietary algorithms to determine the relative concentrations of Hb and Hb-O2, the method is best understood with the basic equation of spectrophotometry, the simplified Beer–Lambert equation: 

\[
A = -\log \left( \frac{I}{I_0} \right) = \varepsilon LC, 
\]

where \( A \) is absorbance, \( I \) and \( I_0 \) are recovered and incident light intensities, respectively, \( \varepsilon \) is the molar absorptivity of the absorbing molecule being measured, at the wavelength of light used, \( L \) is the pathlength of the light and \( C \) is the concentration of the molecule. The reflectance technique does differ from the precise analytical technique applied to cuvettes in a spectrophotometer. Instead of passing through the tissue for complete recovery on the opposite side, the near-infrared light is reflected at tissue interfaces in a banana-shaped arc that is recoverable on the ipsilateral surface with sufficient intensity to trend the concentration of the chromophores being measured. It is not hard to imagine that imperfections in the estimation of pathlength and scatter introduced by reflectance are canceled by expressing the resultant concentrations as a ratio:

\[
\frac{\text{Hb} \cdot \text{O}_2}{\text{saturation}} = \frac{[\text{Hb} \cdot \text{O}_2]}{[\text{Hb}] + [\text{Hb} \cdot \text{O}_2]} 
\]

By comparison to pulse oximetry, cerebral oximeters trend venous-weighted measurements because the entire returned signal is measured rather than just the pulsatile measurements that make pulse oximetry specific to arterial blood oxygen saturation (6). Because cerebral oximetry interrogates all hemoglobin in the reflectance arc (including arterial, venous and capillary hemoglobin), the resulting number is biased toward the larger venous hemoglobin mass, which is consistently higher than, but correlated with jugular venous oximetry (10,11). Where the pulse oximeter is a useful trend of pulmonary function and the a-A gradient, cerebral oximetry trends the ratio of regional oxygen delivery and utilization to detect cerebral ischemia.

**Validation data**

The first validation of any proposed monitoring device is to determine its accuracy. There is no gold standard of tissue oxyhemoglobin content, so jugular venous oximetry is often used as the standard for comparison. In piglet studies measuring both cerebral and jugular oximetry during cardiopulmonary bypass and circulatory arrest, a strong correlation between cerebral and jugular oximetry was reported \((r = 0.91)\) across a full range of jugular saturations (12).

Clinical replication of this animal data has been less consistent. Children and infants have been studied under conditions of cardiopulmonary bypass, extracorporeal membrane oxygenation, and cardiac catheterization. In these clinical scenarios, the jugular oxyhemoglobin content is accessible, so comparisons have been made with cerebral oximetry. An early study of 40 children having a mixture of catheterization and bypass-requiring procedures reported modest correlation \((r = 0.69)\) and a bias of high cerebral oximetry at low jugular oximetry (13). Subsequent studies found higher correlations, similar to the animal data, including a report of 30 children having catheterization and 17 neonates on extracorporeal membrane oxygenation support (10,14).

Cerebral oximetry is a purported measure of oxidative substrate availability to the brain, so an alternative validation standard was the use of mass spectroscopy to measure tissue phosphate energy stores. Reductions in cerebral oximetry have been correlated with reductions in tissue adenosine triphosphate and phosphocreatine (15). There has been little evidence to challenge the claim that cerebral oximetry detects an ischemic milieu in the cerebral cortex. Clinical relevance has been the subject for most of the debate regarding NIRS monitoring.

**Clinical outcome data**

A comprehensive, systematic, and academically rigorous review of the evidence for the use of cerebral oximetry was performed by Hirsch et al., concluding: ‘Although near-infrared spectroscopy has promise for measuring regional tissue oxygen saturation, the lack
of data demonstrating improved outcomes limits the support for widespread implementation’ (16). Noteworthy studies included in this evaluation are summarized below.

Austin et al. performed a nonrandomized, prospective study of multimodal neuromonitoring (including cerebral oximetry), in 250 children during cardiac surgery. Monitoring events were strictly defined and recorded, as well as interventions prompted by the events. When electroencephalogram, transcranial Doppler ultrasonography, and cerebral oximetry were used together, cerebral oximetry accounted for the majority (58%) of monitoring events, with desaturation defined as a 20% reduction from baseline NIRS measurements. Postoperative neurologic sequelae were detected in 26% of patients who had any monitoring event that did not provoke a response. Neurologic sequelae were seen in 6% of patients who had monitoring events that were treated, similar to 7% of patients who had no monitoring event (17).

Dent et al. performed MRI before and 9 days after Norwood procedure in 22 infants with hypoplastic left heart syndrome. Seventy-three per cent of patients had new lesions, or extension of existing lesions, and this was associated with cerebral oximetry readings <45% for >180 min (18). McQuillen et al. performed pre- and postoperative MRI in 53 neonates with congenital heart disease requiring surgery. Overall brain injury was seen in 56% of patients, and low cerebral oximetry during cardiopulmonary bypass was associated with new lesions (19). Phelps et al. studied 50 neonates with hypoplastic left heart syndrome postoperative to Norwood procedure in 22 infants with hypoplastic left heart syndrome. Seventy-three per cent of patients had monitoring events that were treated, similar to 7% of patients who had no monitoring event (17).

A more recent study of 67 infants requiring cardiopulmonary bypass for heart surgery that included pre- and postoperative MRI found no association between cerebral desaturation and new neurologic injuries (21). However, this study was performed at a center that has embraced a ‘goal-directed therapy’ with strategies of bypass and anesthetic care to optimize cerebral oximetry (22). The relatively low incidence of neurologic injury in the study population (36%) cannot be compared to strategies without these adaptations in the absence of randomization.

None of this evidence meets ‘level 1’ requirements to prompt a standard of care, because it is observational, unrandomized, and does not specifically measure the impact of cerebral oximetry monitoring on patient outcome, which would require an inconceivably blinded randomization to include or exclude cerebral oximetry monitoring from care. How have other monitoring devices been evaluated by evidence-based medicine standards? A comprehensive review was made for the Cochrane database, evaluating the more familiar and uncontestedly standard of care pulse oximeter. Studies of pulse-oximetry inclusion and exclusion in perioperative care included data from more than 22,000 patients. Although considered a standard of care by the ASA, the Cochrane database review ‘found no evidence that pulse oximetry affects the outcome of anesthesia for patients’ (7).

Similar stories can be told for other commonly used monitoring devices: The infant cardiorespiratory monitor has not been shown to decrease sudden infant death syndrome, the fetal heart rate monitor has not been shown to change the incidence of cerebral palsy, and the intracranial pressure monitor has not been shown to decrease secondary neurologic injury (6, 23, 24). As with pulse oximetry, there will not likely be a study to conclusively demonstrate that the application of cerebral oximetry improves patient outcomes. Nor will there be a study adequately demonstrating ‘lack of benefit’ to cause rejection of NIRS-based monitoring. Part of the difficulty in demonstrating the value of a monitoring device is that monitoring results can prompt a variety of interpretations and clinical responses (17). It becomes practically prohibitive to recruit a sample size sufficient to account for this variability. Given this limitation, it is more instructive to examine the effect of interventions prompted by monitoring technologies, than to study deployment of the monitor itself.

Goal-directed therapy and NIRS

Cerebral oximetry provides a target for support of oxygen delivery to the brain that is similar to strategies for shock treatment, collectively termed ‘goal-directed therapy’ (2, 25). Therapies promoted by NIRS monitoring of the brain are best understood by examining the determinants of oxygen delivery to the brain. For most organs, oxygen delivery is a function of cardiac output and arterial oxygen saturation. The uneven application of systemic vasoconstriction makes the brain relatively immune to decrements in cardiac output, so cerebral blood flow is a function of cerebral perfusion pressure, not cardiac output (26). Oxygen delivery to the brain can thus be expressed as: 

\[ O_2\text{Del} \propto \frac{\text{CPP} \times r^4 \times [Hb] \times \%\text{Sat}}{\eta} \]

where CPP is cerebral perfusion pressure, \( r \) is the theoretical collective arteriolar resistance vessel radius, [Hb] is the arterial hemoglobin concentration, \( \%\text{Sat} \) is the percentage oxygen saturation of arterial hemoglobin, and \( \eta \) is blood viscosity. Table 1 shows examples of...
how the understanding of oxygen delivery and consumption can prompt interventions when cerebral oximetry is low.

Goal-directed therapy guided by cerebral oximetry monitoring is expected to result in higher pump flow rates during bypass, higher CO₂, a tendency for pH-stat management, and more blood transfusions (27). Further, centers that favor the use of cerebral oximetry are more likely to adopt regional cerebral perfusion techniques as an alternative to deep hypothermic circulatory arrest (22,28). These shifts in practice have been shaped, in part, by the inclusion of cerebral oximetry monitoring in the congenital cardiac operating suite over the last decade as part of a more global effort at goal-directed therapy specific to pediatric cardiopulmonary bypass. The impact of these changes on neurologic outcome is the subject of ongoing trials that require long-term neurologic follow-up.

**Conclusion**

NIRS-based cerebral oximetry is a noninvasive and easily applied monitoring technology that has been shown to trend the oxygen saturation of hemoglobin in the frontal cortex. Based on physiologic principles of oxygen delivery and utilization in the brain, we have outlined and discussed the impact that cerebral oximetry monitoring is having on the care of children with congenital heart disease. We have presented evidence that the cerebral oximeter can detect clinically significant desaturation events that are related to acute brain injury during congenital heart surgery, but similar events in other clinical scenarios for adults, children, and infants remain unclear. The limited data that we have reviewed in this manuscript do not demonstrate conclusively that the application of cerebral oximetry changes patient outcomes, and we have made the argument that such data are unlikely to be obtained without a radical breakthrough in study design methods. Intelligent clinicians have room to disagree on the utility of cerebral oximetry monitoring in anesthesiology practice. Those against routine use of cerebral oximetry in their clinical practice point out the burden of increased patient care costs without level I evidence of clinical benefit. Adopters of NIRS-based cerebral monitoring are not likely to abandon their practice, even understanding the limitations of the supporting data, but this position is consistent with our use of other, more familiar monitoring devices.

The Brain Trauma Foundation faced a similar conundrum when declaring standards for the use of the intracranial pressure monitoring devices. Despite a lack of rigorous objective data to demonstrate that the intracranial pressure monitor changes clinical outcomes, the foundation made a level II recommendation for use of the monitor in cases of severe traumatic brain injury. Further, the foundation indicated in the guideline that efforts to study this question are not likely to be successful and therefore made a relatively strong recommendation without this evidence (6). No drug becomes a recommended therapy without evidence of both safety and efficacy. Why are monitors adopted, and even made standard of care absent this requirement? The answer seems to be more practical than academic. Monitors prompt interventions and can impact the cost of patient care. It is not the monitor itself that changes the patient outcome, but the interventions that result from application of the monitor. There has not yet been a study design that can treat a monitoring device as a standard intervention and measure its effect within constraints of a reasonable sample size. A study of pulse oximetry, for instance, might show benefit if it prompts low-stretch and high end-expiratory pressure ventilation strategies

<table>
<thead>
<tr>
<th>Variable</th>
<th>Clinical scenario causing cerebral desaturation</th>
<th>Intervention</th>
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<tbody>
<tr>
<td>O₂ delivery</td>
<td>CPP Hypotension, elevated ICP, elevated central venous pressure</td>
<td>Maintain ABP above the lower limit of autoregulation. Check venous drainage cannula</td>
</tr>
<tr>
<td>r⁴</td>
<td>Hypocarbia, vasospasm, malpositioned arterial cannulae</td>
<td>Decrease minute ventilation, pH-stat management. Check aortic cannula position</td>
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<tr>
<td>[Hb]</td>
<td>Anemia</td>
<td>Transfusion</td>
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<tr>
<td>% Sat</td>
<td>Cyanosis</td>
<td>Lung recruitment maneuvers, increase FIO₂, manage Qp/Qs ratio</td>
</tr>
<tr>
<td>η</td>
<td>Polycythemia, sickle-cell disease</td>
<td>Partial exchange transfusion, permissive anemia</td>
</tr>
<tr>
<td>O₂ consumption</td>
<td>Fever, seizure, arousal</td>
<td>Cooling, sedation</td>
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</tbody>
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CPP, cerebral perfusion pressure; ICP, intracranial pressure; ABP, arterial blood pressure; r, resistance vessel radius; [Hb], blood concentration of hemoglobin; % Sat, arterial oxygen saturation; η, blood viscosity.
in patients with acute respiratory distress syndrome (ARDS). However, if the same monitor is studied without a concomitant understanding of the mechanism of ventilator-associated lung injury, then it is likely to show significant morbidity. While the pulse oximeter can serve as a guide to ventilator management, it is the ventilator management strategy, and not the pulse oximeter, that ultimately impacts patient outcome. The application of cerebral oximetry is similarly less relevant than the interventions prompted by cerebral oximetry monitoring in relation to outcome.

We are not prepared to stop using the pulse oximeter to guide care for patients with critical respiratory illness. However, examination of practice patterns guided by that monitor is instructive long after it became standard care. Cerebral oximetry monitoring has dichotomized pediatric cardiac care centers, and the preponderance of centers which have adopted the monitor are unlikely to randomize patients to not receive NIRS monitoring. It would be more productive to examine the changes in care introduced by NIRS monitoring than to suggest yet another expensive, underpowered, and inevitably inconclusive study of cerebral oximetry monitoring devices.

Disclosures

Dr. Brady has consulted for Somanetics, Inc. in a relationship that was disclosed and managed by the committee for outside interests at The Johns Hopkins University School of Medicine. This relationship has also been disclosed to the Baylor College of Medicine.

References


Introduction

Survival for children with congenital heart disease requiring operative correction has improved over the last decade because of advances in diagnostic modalities, surgical and cardiopulmonary bypass support techniques, and postoperative management (1). Although mortality is an important outcome, current low rates across institutions make it difficult to use mortality as a measure of performance for quality improvement projects and as an outcome measure for research protocols aimed at developing new management strategies (2). Decreasing mortality has lead to the increased use of in-hospital morbidity as an outcome measure following cardiac surgery for congenital heart disease (3). Morbidity acquired during hospitalization after cardiac surgery may compromise long-term functional status, decrease quality of life, and result in continued resource utilization. Thus, critical evaluation of morbidity acquired during hospitalization after congenital cardiac surgery is essential to compare performance, improve quality of care, and optimize resource utilization. In this review, we explore current mortality rates and factors associated with mortality for children undergoing cardiac surgery in the current era. We will also discuss issues regarding the interpretation and current relevance of mortality as an outcome measure when comparing institutional performance for children undergoing cardiac surgery for congenital heart disease.

Mortality following surgery for congenital heart disease – where are we today?

Admissions and mortality rates from 1992 to 2009 in the Cardiac Intensive Care Unit at Children’s Hospital Boston, Boston, are shown in Figure 1 as an example of improving survival for children with heart disease requiring intensive care. The mortality rate shown in the figure reflects the combined death rates for patients after cardiac surgery (currently 1.8%) and for critically ill patients with congenital or acquired heart disease who have not undergone surgery (currently 4.2%). Current published estimates of mortality rates for children and infants undergoing cardiac surgery vary from 3.7% to 4.3% (2,4,5). Variation in the reported rates
may be as a result of the data source (single institution vs multi-institutional data), type of data set (administrative or cardiac surgery-specific data sets), duration of data collection, and definition of the timing of mortality (30-day mortality vs survival to hospital discharge).

Many advances in imaging technology, surgical techniques, cardiopulmonary bypass, postoperative care, and use of extracorporeal membrane oxygenation to manage refractory cardiorespiratory failure and aid cardiopulmonary resuscitation have all contributed to reduced mortality rates (1,6,7). Survival following all types of congenital heart surgery should be expected despite the increasing complexity of surgical procedures performed. However, it is important to note the relative plateau in mortality rate over recent years (Figure 1), which begs the question as to whether ‘zero’ mortality is attainable. Several patient and non-medical factors make the goal of ‘zero’ mortality elusive.

### Patient factors that increase mortality in children undergoing cardiac surgery

An important determinant of mortality for children undergoing cardiac surgery for congenital heart disease is the complexity of a surgical procedure undertaken. Mortality increases as complexity of the surgical procedure performed increases (8,9). Mortality rates for individual cardiac procedures based on type and procedural complexity have been elegantly compiled by O’Brien *et al.* (4) and range from 0% to 40%. Because mortality rates vary widely depending on procedural complexity, and institutions vary widely in the type of procedures performed (case-mix), comparison of mortality rates between institutions requires the use of procedural complexity-based ‘risk adjustment’ methods to adjust for differences in case-mix among institutions to make interinstitutional comparisons valid. Procedural complexity is thus the basis of the currently used risk stratification systems such as Risk Adjustment in Congenital Heart Surgery-1 (RACHS-1) and Aristotle methods (8,9).

Other risk factors for mortality following congenital heart surgery include neonatal age group, particularly those with birthweight <2.5 kg and/or prematurity, major noncardiac structural anomalies and genetic or nongenetic syndromes, the need for re-operation for a residual cardiac defect, and complications that arise during the postoperative period (Table 1) (8,10–12). In a single institutional analysis of causes of death in children undergoing congenital heart surgery, Ma *et al.* (12) identified that patients who died were commonly

![Figure 1: Cardiac Intensive Care Unit, Children’s Hospital Boston, surgical and nonsurgical admissions and mortality during 1992–2009.](image)

### Table 1 Factors associated with mortality after congenital heart surgery

<table>
<thead>
<tr>
<th>Patient factors</th>
<th>Nonpatient factors</th>
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<tr>
<td>Prematurity</td>
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<td>Staffing and bed occupancy</td>
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<td>Communication</td>
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neonates and infants < 1 year of age, premature newborns, and children with a diagnosis of single ventricle disease. Complications during postoperative care such as need for cardiopulmonary resuscitation and need for extracorporeal membrane oxygenation support were also common occurrences in children who died in this study.

The previously mentioned advances in the field of pediatric cardiac surgery that have improved mortality have also allowed for complex corrective operations in neonates with critical heart disease. As a group, neonates have a higher mortality risk because of their size and increased vulnerability owing to immaturity of organ systems (13–15). In a report of 30-day mortality in 14,843 neonates undergoing cardiac surgery from the European Association for Cardiothoracic Surgery database, the mortality rate was reported as 9.1% (15). In these patients, lower body weight, higher-complexity surgical procedures, longer support times, and single ventricle diagnosis were associated with increased mortality. Similarly, Dorfman et al. (10), in a single-center report of a group of neonates with critical heart disease undergoing cardiac surgery report a hospital mortality rate of 7%, also higher compared to the average mortality rate of all children undergoing cardiac surgery for congenital heart disease. Other nonmedical, but patient-related factors that may influence mortality include race and insurance status (16).

Nonpatient factors that increase mortality

Along with the patient-related factors discussed earlier, several other factors such as institution type, surgical volume, and surgeon experience may influence survival in children undergoing cardiac surgery (Table 1) (17,18). The relative importance of these nonpatient factors compared to patient factors is not clearly known and has been the subject of many recent inquiries. Institutional volume and surgeon experience have been extensively examined in several studies as possible factors influencing mortality following surgery for congenital heart disease. In the mid-1990s, Jenkins et al. and Hannan et al. demonstrated that a volume of cases performed at a center and surgeon experience influenced mortality after congenital heart surgery. Since then, several other investigators have evaluated the volume and mortality relationship in children undergoing cardiac surgery. Using data from the National Inpatient Sample (NIS), a multi-institutional data set containing data on 55,164 surgical procedures during 1988 through 2005, Welke et al. (5,19) showed that large volume centers (> 200 cases per year) outperformed all other centers after adjusting for differences in case-mix among the centers studied. Another report by Welke et al. (2) using data from 32,413 patients from 48 institutions in the Society of Thoracic Surgeons Congenital Heart Surgery Database reported more recently (2002 through 2006) demonstrated that center volume was inversely related to mortality rate when all procedures were compared together. Mortality was shown to be considerably lower in large volume centers performing ≥350 cases per year for complex procedures (Aristotle difficulty > 3.0) compared to centers performing < 350 cases per year (14.8% vs 8.4%). However, for low-complexity procedures (Aristotle difficulty ≤ 3.0), there was no difference in mortality among centers. Thus, it is possible that increased experience and improved perioperative care in low volume centers may have largely neutralized the effect of institutional case volume on mortality for less-complex surgical operations. The influence of high level of scrutiny from regulatory agencies, public reporting of center-specific survival rates, and consumer expectation of improved performance for low volume centers may have led to improved outcomes. However, the significance and influence of these issues on improved outcomes in low volume centers are difficult to estimate.

Whether an upper threshold exists in high volume centers beyond which operative mortality may actually increase is another area for evaluation in the future. Increasing case volume can exceed the resources available in a system, resulting in decreased quality of care from overscheduling, need for rapid turnover resulting in increased re-admission rates, and increased errors related to human factors such as fatigue and poor communication. Defining the threshold beyond which quality of care may decrease in high volume centers may be important in guiding future regionalization, more appropriate distributing work load, improving quality of care, and sustaining reduction in the mortality rate for congenital heart surgery in the future.

In addition to volume and center characteristics, technical performance of the surgeon and adequacy of repair after an operation have also been shown to influence mortality for children undergoing complex cardiac surgery (20–22). In a recent report, Karamichalis et al. (22) assessed the influence of a technically optimal operation compared to a technically adequate or inadequate operation on mortality following the stage I palliation of hypoplastic left heart syndrome. They showed that a technically optimal procedure neutralized the effect of poor preoperative physiological status and contributed to reduced hospital mortality. In another report, Karamlou et al. evaluated the influence of institutional and surgeon experience,
patient management, and patient demographic factors on mortality following congenital heart surgery for four groups of neonates undergoing palliative or reparative procedures for a transposition of the great arteries, pulmonary atresia with intact ventricular septum, interrupted aortic arch, or the Norwood operation (23). They demonstrated that for some procedures (Norwood and pulmonary atresia with ventricular septal defect), institution or surgeon experience did not influence mortality; rather patient and postoperative management issues were important. However, in the group of patients undergoing repair of transposition of the great arteries, institution and surgeon experience rather than patient factors influenced mortality. Thus, the influence of institution and surgeon factors on mortality may vary based on the procedure and may not affect outcomes for all surgical procedures. Furthermore, this study also demonstrates that in some cases mortality may be strongly influenced by patient and postoperative management factors rather than by technical outcomes of the procedure itself. Although research has focused on surgeon performance, the contribution of the performance of other caregivers including anesthesiology, cardiology, and intensive care teams toward errors in diagnosis, decision making, and communication has not been evaluated and should be the focus of future research.

**Mortality as an indicator of quality of cardiac surgical programs**

In-hospital mortality is frequently cited as a measure to compare the performance of cardiac surgical programs for purposes of research, as well as by external agencies and regulatory bodies (2). The use of mortality as a discriminator of quality stems from the adult cardiac surgical experience where mortality has been shown to accurately reflect quality. This is directly related to the availability of a large volume of adult cases for comparison, the relative uniformity of adult cardiac surgical procedures, and the availability of robust risk adjustment systems. In comparison, fewer children undergo cardiac surgery, and center volume and case complexity can vary widely between centers. Adding to these factors, low mortality rates make comparison of institutional performance based on mortality difficult.

Welke et al. (2), in a 2010 report, using data from 21,709 operations from the NIS data set demonstrated that pediatric surgical volume in centers performing cardiac surgery was too small to effectively show differences in mortality rate for assessing institutional performance. Furthermore, the authors correctly conclude that the absence of differences based on low volume may falsely reassure small-volume centers that their performance is no different than the mean. Because of the many limitations of mortality as an outcome measure as outlined here, the use of other morbid events that occur with higher frequency, such as postoperative complications, neurological outcomes, and length of hospitalization to better reflect institutional performance should be considered in the future (24). These morbid events may decrease functional status and quality of life for those surviving to hospital discharge after congenital heart surgery and thus also influence long-term outcomes and resource utilization. Future research directed at studying the use of morbid events as an outcome measure following congenital heart surgery may help better define an optimal measure that is relevant and useful for designing interventions that can help promote quality of care as well as long-term outcomes.

**Summary**

Mortality for children undergoing cardiac surgery is low in the current era. Neonates, children with major noncardiac structural anomalies, and children undergoing high-complexity cardiac surgical procedures may have increased mortality. Studies aimed at improving mortality for cardiac surgery in children with heart disease should potentially target these populations. Although it is necessary to continue to monitor mortality in children undergoing cardiac surgery, low mortality rates and need for improved quality of life and functional outcomes in survivors demand that we define other relevant outcomes measures for the future.

**References**


5 Welke KF, O’Brien SM, Peterson ED et al. The complex relationship between pedi-