Anesthesia Considerations for Pediatric Thoracic Solid Organ Transplant

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Alexis Carrel is known as the founder of organ transplantation and was awarded the Nobel Prize in Medicine and Physiology in 1912 for his pioneering work \cite{1}. There followed a 20-year hiatus before further techniques of organ transplantation were refined and almost 50 years before the definitive work on cardiac allograft rejection and its grading were reported by Margaret Billingham. The first pediatric heart transplantation was performed on December 6, 1967, by Kantrowitz, and the first successful clinical cardiac transplant in a child was performed by Denton Cooley in 1968. Lower and Shumway, from Stanford University, are recognized for their impressive work on advancing the surgical techniques for heart transplantation and for recognizing that immunologic barriers were the main obstacles to advancing clinical cardiac transplantation. Thoracic organ transplantation, although still largely palliative in children, offers the only hope of survival in the recipient.

Indications for heart transplantation

Over the last decade, the number of heart transplants performed in patients 17 years and younger has remained steady. The annual report of the registry for the International Society for Heart and Lung Transplantation is a comprehensive source of information on solid thoracic organ transplantation in children \cite{2}. The
infant age group features prominently compared with other recipient age groups, and the most common indication for transplantation is congenital heart disease (CHD) (67%). In the older children (1–10 years old), cardiomyopathy accounts for 50% of heart transplants, and this percentage increases to 60% in the 11- to 17-year-old group. Infants who undergo transplantation in the first year of life may require retransplantation in approximately 10 years.

**Recipient evaluation for heart transplantation**

Before placing a child on the transplant list, suitability is determined. Pre-existing renal and liver failure, infections, and social and psychologic issues may preclude transplantation. Cardiopulmonary assessment includes cardiac catheterization and angiography. The former assessment determines pulmonary artery pressures and calculates pulmonary vascular resistance (PVR) and, if elevated, whether it is reversible with oxygen and or nitric oxide. Pulmonary hypertension with a PVR level greater than 5 Woods U/m² is associated with increased mortality [3]. In addition, this information is valuable in donor selection (a larger heart) and in considering heterotopic heart transplantation, allowing the donor heart to beat in tandem with the recipient heart (described later). Angiography is important to clearly define the vascular connections because this will have implications during surgery; for instance, if the patient is an extracorporeal membrane oxygenator (ECMO) survivor, the right internal jugular and carotid arteries may both have been ligated. In addition, in children who have undergone repair of CHD, the pulmonary artery anatomy may be distorted. In addition to assessing the cardiac and pulmonary function, hepatic synthetic function also must be evaluated. Because of chronic hepatic congestion and nutritional deficiency secondary to heart failure, coagulation factors may be abnormal, which will have a significant impact on bleeding after the transplant.

**Donor selection**

The United Network for Organ Sharing lists recipients awaiting transplants in three categories, 1A, 1B, and 2, in which 1A patients are the sickest and in need of an urgent transplantation. When a donor becomes available, the list is checked for suitable recipients. Organ procurement is coordinated by local government-regulated agencies. Pediatric patients account for 5% to 7% of all of the patients awaiting heart transplant, and 40% of those patients are in the range of 1 to 5 years old [4]. For children older than 1 year of age, the median time on the waiting list is 3 months; however, among the infants listed, the death rate is six times that in other pediatric age groups and 10 times the overall cardiac waiting list mortality. Although ABO blood group compatibility is an important consideration in donor matching for improved allograft survival in the recipient, many centers are crossing the blood group compatibility barrier, particularly for infants. In such
cases, plasma exchange should be performed during cardiopulmonary bypass (CPB) to reduce iso-hemaglutinin levels, which reduces the risk of allograft rejection. Packed red blood cells (PRBC), used in priming, must be ABO-compatible with the recipient. All plasma components and platelets must contain no anti-A or anti-B antibodies to the donor or recipient [5]. Early results are encouraging, perhaps related to a poorly established immune system in neonates and infants [6].

HLA matching is not performed routinely because of time constraints, even though graft survival is improved with HLA-matched donors. Instead, panel reactive antibodies (PRA) are assayed. PRA are circulating HLA alloantibodies. Although elevated PRA do not preclude heart transplantation, there is a greater risk of allograft rejection. Furthermore, in children who have PRA levels greater than 10%, the overall mortality has been found to be higher than in those with lower PRA [7]. This preoperative information is important in the choice of immunosuppression and other therapies such as plasmapheresis or intravenous (IV) immunoglobulin to reduce PRA levels. The weight match between donor and recipient also is a consideration, and the donor usually is 80% to 160% of the recipient’s body weight, with the larger organ directed toward infants or children who have pulmonary hypertension. Although a long donor ischemia time (eg, greater than 6 hours) may not be ideal, such prolonged ischemic time is not a risk factor for decreased long-term survival; hence, the procurement of hearts with prolonged donor ischemic time may be justified in the setting of an increasing recipient pool with a fixed donor population [8,9].

**Intraoperative management**

Children listed for heart transplants have experienced several hospitalizations and often have been exposed to several anesthetics. It is essential to review previous medical records and the most recent diagnostic data. Many of these patients, particularly those who have undergone previous surgeries for CHD, might have had arterial and venous cut-downs. This information is important in planning vascular access for the transplant. Some children may be in the intensive care unit, already on mechanical cardiac support as a bridge to transplantation or be intubated and ventilated for management of their heart failure. Yet others may be at home and might have eaten recently. In most instances there is enough time between a patient receiving notification of the transplant and entering the operating room that the nothing-by-mouth (NPO) status is not an issue. If it is, then rapid sequence induction might be necessary. For children who have elevated PVR and those who have been on prolonged ventilatory support, the present authors set up nitric oxide in the operating room for use while weaning the patient from CPB.

Because of prolonged illnesses and several hospitalizations, these children may not separate easily from their parents without a premedication. Other in-
vestigators have described their experiences with the anesthetic management [10,11].

The present authors’ preference is to administer midazolam for premedication, either orally (0.5–1 mg/kg) or through an existing IV line (0.05–0.1 mg/kg). If administered IV, the patients should be monitored with a pulse oximeter, and equipment for resuscitation must be at hand. Ketamine (0.5–1.0 mg/kg, IV) is also suitable. Following routine noninvasive monitoring in the operating room and preoxygenation, if anesthetic induction is performed intravenously, etomidate or ketamine or fentanyl and muscle relaxant is used. Propofol must be used judiciously [12]. Inhalation induction with sevoflurane in 100% oxygen is recommended for those patients without intravenous access. Following induction and intubation, mechanical ventilation is instituted followed by the insertion of invasive monitoring lines. Because of the immunosuppressive therapy after transplantations, all access, including peripheral intravenous catheters, must be placed with proper aseptic precautions. It is institutional protocol to insist on a sterile gown and gloves for central line access. The present authors routinely cannulate the internal jugular vein for central access and place a double-lumen catheter both for monitoring central venous pressure and for the administration of inotropic agents, after weaning the patient from CPB. A transesophageal echocardiography (TEE) probe is placed for monitoring. Antifibrinolytics are reserved for patients who have previously undergone heart surgery for CHD or in those with prolonged preoperative prothrombin and or partial thromboplastin time or thrombocytopenia. Management on cardiopulmonary bypass is the same as for other open-heart surgery. Surgery usually is performed under conditions of moderate hypothermia (28°C), with the orthotopic transplantation technique described by Lower and Shumway [13]. In children who have had previous heart surgery, greater technical challenges exist [14].

Weaning a patient from CPB often involves instituting inotropic support with low-dose dopamine (3–5 μg/kg/min) and milrinone (0.5 μg/kg/min). The latter has salutary effects on PVR. Mild hyperventilation (PaCO₂ in the mid 30-mmHg range) will also reduce PVR. If the right heart appears distended and ventricular function on TEE is sluggish, then direct pulmonary artery pressure can be measured, and nitric oxide can be added if the mean pulmonary artery pressure exceeds 25 mm Hg; a dose of 20 to 40 ppm usually is adequate [15]. If, despite adequate inotropy, myocardial function remains poor, mechanical support such as a right ventricular assist device or ECMO may be necessary [16]. The transplanted heart is denervated; hence medication such as atropine, which acts through the vagus, will have no effect on the heart rate [17]. Myocardial α and β receptors present in the donor heart respond appropriately to direct-acting agents such as epinephrine. Although two P waves are visible on the electrocardiogram, only the donor heart P wave is conducted to the atrioventricular (AV) node and is responsible for heart rate. If the heart rate is slow, temporary pacing may need to be instituted in addition to the use of chronotropic agents. Once a stable hemodynamic state is established, heparin is reversed with protamine, and after adequate hemostasis, immunosuppressive agents are administered per protocol.
Immunosuppressive agents

Immunosuppressive agents can be divided broadly into the following categories: (1) broad-spectrum agents such as corticosteroids; (2) calcineurin inhibitors (eg, cyclosporine and tacrolimus); (3) anti-interleukin 2 receptor (IL-2R) antagonist (eg, daclizumab); (4) antiproliferative agents (eg, azathioprine and mycophenolate mofetil [MMF]); (5) rapamycin inhibitors (eg, sirolimus); (6) monoclonal antibodies against CD3 (eg, T lymphocytes:muromonab-CD3 [OKT3]); (7) polyclonal antibodies against T cells (eg, anti-thymocyte gamma globulin); and (8) other modalities such as plasmapheresis and lymphoid irradiation [18].

Postoperative immunosuppression can be divided into induction and maintenance phases. Cyclosporine or tacrolimus is the first-line drug. The cyclosporine dosage is adjusted to obtain serum trough levels of 200 to 300 ng/mL. MMF, azathioprine, an IL-2R agent such as daclizumab, and prednisone are added (four-drug therapy). OKT3 has considerable side effects, and its use has declined in pediatric patients [2]. Because of their long-term side effects, corticosteroids are tapered and reinstituted only when rejection is suspected or proven. Although it may seem intuitive, induction therapy does not reduce the frequency of rejection or survival.

Outcome after heart transplantation

Currently, the 1-year survival rate after heart transplantation is 90% for all children and 85% for infants. Although in infant recipients the early mortality is greater, 50% of patients survive 13 years or longer. This is longer than that in older children and adolescents [2]. Risk factors for mortality within 1 year are summarized in Table 1. Donor ischemia time is not a risk factor for early mortality. At 5 years, the contribution of diagnosis leading to transplantation, the clinical status at transplantation, and the need for dialysis continue to be significant. Interestingly, the recipient’s need for ECMO before transplantation or hos-

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds ratio</th>
<th>P value</th>
<th>95% confidence interval for odds ratio</th>
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<td>&lt;.0001</td>
<td>2.08–4.00</td>
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<tr>
<td>Other diagnosis (excluding cardiomyopathy)</td>
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<td>.007</td>
<td>1.26–4.39</td>
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<td>1.13–4.53</td>
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<tr>
<td>On ventilator</td>
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<td>.0005</td>
<td>1.30–2.52</td>
</tr>
<tr>
<td>Hospitalized (including intensive care)</td>
<td>1.60</td>
<td>.003</td>
<td>1.17–2.18</td>
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Hypertension occurs in almost half of the recipients within the first year, followed by hyperlipidemia (10%) and renal dysfunction (5%), and by 5 years the
prevalence of these morbidities increases with coronary vasculopathy in 10% or more, which increases to 14% by 7 years. The use of prednisone is associated with the early development of hypertension. Growth retardation and psychiatric illnesses can further affect the quality of life [19]. However, at 7 years, ≥ 95% of patients show no limitation of activity.

The authors’ institution (Stanford University) reviewed 52 patients who survived more than 10 years after transplantation and reported an actuarial survival rate of 79.4% at 14 years and 53.1% at 20 years. At their last evaluation, 71% of patients were receiving a cyclosporine-based regimen; 23% were receiving a tacrolimus-based regimen; 33% were steroid free; 42% were totally free from treatable rejection; 44% developed serious infections; 69% were receiving anti-hypertensive agents; and 8% required renal transplantation. Neoplasms occurred in 23%, graft coronary artery disease (CAD) occurred in 25%, and 15% of the patients underwent retransplantation. For 12 patients who died, CAD was the most common cause of death, followed by nonspecific late graft failure. Physical rehabilitation and a return to a normal lifestyle was nearly 100% (Daniel Bernstein, MD, personal communication, 2005).

Rejection

Rejection episodes may occur in asymptomatic patients or present with a variety of clinical signs. Endomyocardial biopsy is the gold standard for diagnosis, which is then graded from 0 to 4 based on histopathology. Patients who have grade 3 rejection receive an intensified immunosuppressive therapy. The data from echocardiography alone cannot accurately identify clinically important episodes of rejection [20]. Children presenting for endomyocardial biopsy when rejection is suspected might have poor myocardial function. Sedation and anesthesia must be used cautiously with appropriate monitoring and care.

Lung transplantation

Children destined for lung transplantation are likely to undergo surgical procedures before and after transplantation. Anesthetic management of these pediatric patients requires an appreciation of the challenges presented by end-stage lung disease, lung transplantation, and life-long immunosuppression.

History of lung and heart–lung transplantation

Dimikhov performed the first canine orthotopic heart–lung (1946) and orthotopic lung transplants (1947). The first human lung transplant was accomplished in 1963 by Hardy. Shinoi performed the first human lobar transplantation (1966), and Cooley performed the first clinical pediatric heart–lung transplant in

In contrast, the outcome after lung transplantation was uniformly bleak until the early 1980s. One of the main problems was failure of the bronchial anastomoses. Work by Pearson and Cooper [1] has shown that immunosuppressive steroids impair bronchial healing. Fortunately, the new immunosuppressive cyclosporine was found to preserve anastomotic tensile strength. Additionally, the use of bronchial omentopexy resulted in the development of collaterals that achieved arterial circulation to the bronchus within 4 days. The Toronto group performed the first long-term successful single-lung transplant in 1983. The first living-donor lobar transplant was performed at Stanford by Starnes in 1990.

**Number of procedures**

Lung transplantation remains an uncommon procedure in the pediatric age group. The incidence of lung transplantation in children is less than one per million population. Data from the International Society of Heart Lung Transplantation and the United Network for Organ Sharing indicate that fewer than 5% of lung transplant recipients were younger than 18 years of age [2,21]. The majority of pediatric recipients are in the 11- to 17-year-old age group [22]. Very few pediatric centers perform more than four lung or heart–lung transplants per year [21]. During the period 2000 to 2002, the number of pediatric solid organ transplants reported in the United States was 420 liver, 289 kidney, 273 heart, 61 intestine, 43 lung, and 6 heart–lung transplants [21]. Thus, although pediatric lung transplantation has been established as an accepted therapy, the number of listed patients and the number of active centers lag behind adult lung transplantation and other pediatric solid organ transplantations.

**Waiting list**

The selection criteria for pediatric lung transplantation donors include ABO blood group compatibility; negative HIV serology; a $\text{PaO}_2 \geq 350 \text{ mm Hg}$ when ventilated with $\text{FiO}_2 = 1.0$; clear chest radiograph; no evidence of airway erythema; minimal leukocytes and pathogens in the sputum; no evidence of contusion by gross inspection; and a reasonable donor–recipient size match [23,24].

The average time waiting for cadaveric lungs varies with the recipient’s age and is currently 20 months for teenagers, 14 months for children 6 to 10 years old, 4 months for children 1 to 5 years old, and 1 month for infants [25]. Approximately one third of listed children die before transplantation [26], reflecting
the severity of illness for which these candidates are being listed, as well as the paucity of suitable donor organs.

Several strategies have been devised to increase the availability of donor lungs. Aggressive management with invasive monitoring, fluid restriction, diuretics, inotropes, and steroids can permit the harvest of functional lungs from donors who were classified previously as unacceptable. Survival at 1 year after surgery was not different from that of patients receiving lungs from donors who met standard criteria [27]. The extension of the ischemia time beyond the generally accepted limit of 8 hours may be possible as preservation techniques improve. Successful transplantation of lungs from a non-heart–beating donor has been performed [28], but concerns about warm ischemia time and organ preservation are significant.

Another option is the acceptance of greater size disparity between donor and recipient. Small donor lungs transplanted into large thoracic cavities present no problems for the recipients because lung expansion and diaphragmatic elevation combine to fill the entire chest cavity. Large donor lungs require lung reduction techniques such as stapling along the fissures, lobectomy of the transplanted lung, or partitioning of the left donor lung with transplantation of the lower lobe in the left hemithorax and the upper lobe in the right hemithorax [29]. Intermediate results suggest patient survival rates comparable to those of patients who have received organs from size-matched donors. Pulmonary vascular resistance may increase if the transplanted pulmonary vascular bed is small relative to the recipient’s cardiac output. Acute right heart failure can be avoided by using cardiopulmonary bypass and nitric oxide [29].

Living-donor lobar lung transplantation is an alternative treatment offered to patients who meet the standard criteria of cadaveric lung transplantation [30]. For patients requiring bilateral lung replacement, two separate donors are required. Each of the donors supplies a lobe, either the right or left lower lobes. More than 90% of patients receiving lobar transplantation have cystic fibrosis because they tend to be of small stature, allowing two lobes from average-sized adult donors to provide sufficient pulmonary tissue. The benefits of living-donor transplantation are that the donor’s medical history is well known, ischemic time is kept to a minimum, and rejection episodes are likely to be unilateral and less severe than those patients receiving cadaveric lung tissue. The donor lobes usually are able to accommodate the full cardiac output without a significant incidence of right heart failure. Because of the risk to the donors, living-donor transplantation is currently considered only for patients who have significant clinical deterioration.

**Indications for lung transplantation**

The diseases for which lung transplantation is performed vary with patient age (Table 2) [2,31]. Pediatric and adult criteria for lung transplantation are
similar: listing should be considered when an individual is at risk of dying from lung failure or pulmonary vascular disease and/or has a poor quality of life despite maximal medical therapy. Generally, children are listed if they have less than a 50% chance of surviving for another 2 years. Children who have cystic fibrosis, who have forced expiratory volume (FEV)\textsubscript{1} ≤ 30%, PaO\textsubscript{2} ≤ 55 mm Hg, or PaCO\textsubscript{2} ≥ 50 mm Hg, were reported to meet these criteria [32]. The majority of older children listed for transplantation can live at home. Infants usually are in intensive care, on maximal ventilator therapy, and perhaps ECMO support. Heart–lung transplantation is indicated in patients who have end-stage lung disease or pulmonary vascular disease in patients who also have irreparable heart defects or left ventricular failure. Patients who have primary or secondary pulmonary hypertension and right heart failure often have resolution of cor pulmonale with lung transplantation alone.

**Contraindications for lung transplantation**

Currently, most contraindications are relative (Box 1). Transplantation is deferred when active viral infection is present. Likewise, clinical outcome is poor when cystic fibrosis patients are infected with *Burkholderia cepacia*, especially subtype genomovar-3 BCC.

Previous thoracotomy, tracheostomy, and chemical pleurodesis are not considered contraindications. Abnormalities such as tracheomalacia may complicate airway anastomoses, and multiple aortopulmonary collaterals in association with tetralogy of Fallot/pulmonary atresia may frustrate reconstruction of the pulmonary arteries. Cystic fibrosis patients who have end-stage hepatic and lung disease have successfully undergone combined liver and lung transplantation. Noncompliance with medical therapy can be a contraindication. In such cases, a signed contract of listed expectations may allow probational listing for transplantation [21].
Transplantation procedure

Most children undergo bilateral sequential lung transplantation through a bilateral anterolateral clamshell thoracotomy. Cystic fibrosis affects both lungs; very few pediatric single-lung transplants are performed. Cardiopulmonary bypass with moderate hypothermia (28°C) is used for almost all cases because it allows the native lungs to be deflated, thereby facilitating their surgical removal. This reduces the donor lung ischemia time and permits clamping and antibiotic irrigation of the tracheobronchial airway. Additionally, double-lumen endobronchial tubes will not fit into younger children, and many pediatric recipients are too sick to tolerate one-lung ventilation. The disadvantages of CPB include the

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**Box 1. Medical and surgical contraindications to pediatric lung transplantation**

**Absolute**

- Severe scoliosis or thoracic cage deformity
- Severe tracheomegally or tracheomalacia
- Hepatic, renal, and left ventricular failure (multiorgan transplantation, such as liver–lung, renal–lung, or heart–lung transplantation might be an appropriate option)
- Severe transpleural systemic-to-bronchial artery collateral arteries
- *Burkholderia cepacia* genomovar-3 lower respiratory infection
- Active malignancy
- HIV infection
- Active viral infection
- Active mycobacterial infection
- Bacteremia and septicemia
- Irreversible and significant respiratory muscle dysfunction

**Relative**

- Symptomatic osteoporosis or osteopenia
- Pneumonectomy (unless volume-occupying device is in place)
- Panresistant microorganisms within the respiratory tract
- *B. cepacia* genomovars (other than genomovar-3) lower respiratory infection
- Daily systemic corticosteroids
- Severe malnutrition

deleterious consequences of the systemic inflammatory response that it initiates and the requirement for anticoagulation.

After CPB commences, the recipient’s lungs are removed, and the right and left donor lungs are implanted using end-to-end bronchial anastomoses. Peribronchial tissue is sutured loosely around the bronchial anastomoses to provide blood flow by new vessel in-growth. The pulmonary artery and vein connections are performed. A donor atrial cuff is attached to the recipient’s left atrium, taking care to avoid suture lines near the pulmonary veins, thereby reducing the risk of pulmonary vein stenosis. A central venous catheter for long-term IV therapy is often placed at surgery [21]. Living-donor lobe transplantation requires three surgeries to be undertaken simultaneously (two donors and recipient) to minimize ischemia times. Such procedures can be very resource-intensive.

Preoperative evaluation

Candidates for lung transplantation are subjected to extensive medical and social evaluations. Many undergo cardiac catheterization to define anatomy and pathophysiology. If pulmonary vascular resistance is elevated, the responses to nitric oxide, oxygen, and other vasodilators are noted. After being listed for transplantation, the patient should be scheduled for elective assessment by the anesthesia transplant team. Relevant data are reviewed, the patient is examined, and an anesthesia plan is discussed with the child and the family.

Anesthesia management

Once transplantation is scheduled, an urgent reevaluation of the patient’s status by an anesthesiologist is necessary to update and finalize the anesthesia plan. Attention should be paid to the patient’s current medication regimen, when the child last fed, and any necessity for preoperative intravenous access. If prostacyclin is being administered, it requires a dedicated intravenous line because of incompatibility with other intravenous agents. The patient’s preferred posture when resting may indicate optimal patient positioning for preserving respiratory function during anesthesia induction.

Benzodiazepine anxiolytic agents (eg, midazolam) may be useful preoperatively, but discretion is advised because of the potential for compromise to upper airway control, respiratory effort, and hemodynamic stability; premedication should probably be avoided in a nonmonitored setting.

Anesthesia preparations are similar to those for pediatric hypothermic open-heart surgery and include provision for the rapid infusion of fluids, manipulation of body temperature, rapid laboratory tests, immediate availability of blood products, echocardiography, and specialized monitoring modalities.
The method of anesthesia induction and choice of agents will depend on the patient’s clinical and NPO status [33]. The hemodynamic goal is to preserve stability without increasing pulmonary vascular resistance. Both volatile and intravenous anesthetic agents are acceptable. Ketamine has been used successfully in patients who have poor cardiac reserve and/or pulmonary hypertension. Ketamine reportedly does not increase pulmonary artery resistance in children, but this may not always be the case [34]. Anesthesia and positive pressure ventilation may unmask a relative intravascular volume deficiency that can be corrected by IV fluid infusion. Anesthesia can be maintained by narcotics (eg, fentanyl), benzodiazepines, and volatile agents (eg, isoflurane) and titrated to the patient’s hemodynamics. Nitrous oxide is best avoided because of concerns about myocardial depression, pulmonary hypertension, air embolism, and the requirement for high concentrations of inspired oxygen.

Invasive monitoring appropriate for surgery with CPB is established. In cases in which pulmonary hypertension is of concern, a pulmonary artery catheter can be placed through a sheath in the internal jugular vein before the patient is weaned from CPB. Alternatively, especially in small children, the surgeon can insert a transthoracic catheter directly into the pulmonary artery. Intraoperative transesophageal echocardiography is useful for assessing cardiac function, intracardiac structures, pulmonary hypertension, and blood flow at sites of potential stenoses.

The airway is secured with a single-lumen endotracheal tube because CPB obviates any requirement for lung isolation. Frequent toilet of the airway is advised, particularly in patients who have cystic fibrosis. Bronchodilator therapy should be available. Effective oxygenation and carbon dioxide elimination may be difficult during the pre-CPB period, and permissive hypercapnia is acceptable. Ventilation should be adjusted to minimize air trapping because lung hyperinflation can impede venous return to the heart. Occasionally, especially in infants, a sophisticated pediatric intensive care ventilator may be required in the operating room. Many patients who have end-stage lung disease have a chronic compensatory metabolic alkalosis. Enthusiastic hyperventilation to normal PaCO₂ values induces an iatrogenic alkalotic blood pH level that increases cerebral vasoconstriction and leads to relative cerebral ischemia.

Knowledge about the donor’s medical course may help predict the function of the transplanted lungs. The function of the implanted lungs could be affected adversely by ischemia, reperfusion injury, cardiopulmonary bypass, denervation, lymphatic stasis, and hyperacute rejection, resulting in hypoxia and reduced lung compliance from pulmonary edema and pulmonary hypertension. Before weaning from CPB, the lungs are carefully re-expanded and checked for bronchial air leaks. Ventilation is adjusted to achieve satisfactory gas exchange while minimizing baro-trauma. If possible, inspired oxygen concentrations should be lowered because of the concern about oxygen toxicity and free-radical damage [35]. Flexible bronchoscopy may be used to inspect the bronchial anastomotic sites. Usually, minimal inotropic support is required during the post-CPB period but depends on the patient’s cardiac status.
Children undergoing lung transplantation are at risk for perioperative bleeding because: (1) CPB was used; (2) the presence of chest wall adhesions from infection (cystic fibrosis) or previous surgery; (3) the presence of abnormal vessels such as aortopulmonary collaterals; and (4) cyanosis, which has multiple deleterious effects on coagulation. Aprotinin, a serine protease inhibitor, is often administered prophylactically [36] but carries some risk of anaphylaxis [37].

Intraoperative antibiotic and immunosuppressive therapies are administered according to the institution’s protocol. A regimen of cyclosporine or tacrolimus and corticosteroids is often started before surgery [21].

**Postoperative course and pain management**

Patients are sedated and on ventilator support when they are admitted to intensive care for postoperative care. Older patients who have cystic fibrosis have been weaned from ventilation after 3 days (range 1–47) and discharged from intensive care after 5 days (range 1–53) [38]. Infants may have complex clinical problems and are often critically ill before surgery. They required ventilation for a longer time (24 ± 19 days) and stayed in intensive care for an extended period (56 ± 33 days) [39].

In the early postoperative period, pain relief can be provided with IV narcotic infusions. Adjuvant analgesic medications may include ketorolac (if bleeding is no longer a concern) and ketamine. When appropriate, patient-controlled analgesia can be offered. Benzodiazepines are useful when sedation is indicated. Regional analgesia would seem an attractive pain management option for older children who have satisfactory postoperative lung function, in whom successful early extubation of the trachea is feasible. Potential advantages include earlier mobilization of the patient and a shortened period when airways are subjected to an endotracheal tube and positive pressure ventilation. However, the emergent nature of lung transplantation surgery and the necessity for anticoagulation with CPB complicate the option of thoracic epidural analgesia because of the concern about bleeding complications. Careful analysis of the benefits and hazards of this type of therapy is required. Older patients undergoing scheduled living-donor lung transplantation may be candidates for thoracic epidural placement on the day before surgery. Alternatively, an epidural catheter may be placed postoperatively, after the coagulation profile has normalized. Intraoperative placement of thoracic epidural catheters before incision has been reported in children undergoing lung transplantation (Laura Diaz, MD, personal communication, 2005). However, if catheter insertion has resulted in bleeding of concern, delaying surgery would be an unpopular option because of prolongation of donor lung ischemia time.

Transplantation results in vagal denervation of the lungs, manifested by a decreased response to hypercapnea, resting bronchodilation, decreased pulmonary clearance of secretions, and a less effective cough. Denervation also leads to...
the loss of afferent stimuli to the respiratory center and poor coordination between thoracic and abdominal respiratory muscles. Transplanted lungs have no lymphatic drainage and are more susceptible to pulmonary edema and clear such edema more slowly. The increased water content lowers lung compliance [35,40,41].

Evidence from infant spirometry and serial CT scans suggests that transplanted lung growth of the alveoli and airways occurs with somatic growth in children [42,43]. Transplanted adult lobes grow in size, but the increase is from alveoli distension rather than from an increase in the number of alveoli [23].

Many children who have end-stage lung disease such as cystic fibrosis are malnourished and have stunted skeletal growth. After transplantation, steroid immunosuppression commonly leads to a rate of growth that remains below the age-adjusted normal range. Administration of growth hormone is selected cases may be effective [21].

### Immunosuppression and surveillance

Most centers use a three-drug immunosuppressive regimen consisting of a calcineurin phosphatase inhibitor such as cyclosporine or tacrolimus, a purine synthesis inhibitor (azathioprine or mycophenolate mofetil), and a corticosteroid. Initially, cyclosporine or tacrolimus is administered intravenously, with conversion to an oral medication when gastrointestinal function returns. Drug doses are adjusted according to trough or peak blood levels. Patients who have cystic fibrosis require close monitoring of cyclosporine levels because of unreliable drug uptake and variable hepatic clearance. Previously, azathioprine was administered as a second agent, provided white cell counts were acceptable, but MMF has recently become preferred over azathioprine [2,44]. Some centers add the monoclonal antibody daclizumab for induction therapy [31]. Corticosteroid regimens vary between institutions, but early postoperative dosing with methylprednisilone, 0.5 to 1.0 mg/kg/d, orally, tapering to 0.25 to 0.5 mg/kg/d after 3 months, is typical [21]. In contrast to immunosuppressive therapy for heart transplantation, steroid therapy is often continued long-term, sometimes as alternate day therapy.

Patients are monitored closely for rejection and infection. Pulmonary function tests are performed at regular intervals to monitor lung function and growth. Periodic bronchoscopy and transbronchial biopsies are also scheduled [31].

### Post-transplantation considerations and complications

Anesthetic and perioperative management of pediatric organ recipients in nontransplant surgery was reviewed recently [45]. The most common compli-
cations after lung transplantation fall into three general phases (Table 3) and, if present, may alter anesthesia care [25].

Rejection

Hyperacute rejection results from previous exposure to foreign tissue antigens so that recipient antibodies bind to donor tissue antigens and cause complement-mediated graft injury. A panel reactive antibody test identifies patients at risk. This rare, early complication usually is controlled with plasmapheresis and cyclophosphamide (Cytoxan) therapy, but it can result in graft loss [46].

Acute rejection presents later and is recognized histologically by perivascular lymphocytic cuffing in the small graft vessels. Acute rejection may be asymptomatic or present with nonspecific symptoms or mimic infection, with fever, dyspnea, and hypoxia. It appears that young children may have a lower risk of rejection compared with older children and adults, perhaps because the immune system of infants is relatively immature [31,47–49]. Spirometry is used for assessing graft function and, when modified, may be applicable in children as young as 2.5 years of age [50]. Any clinical suspicion of rejection, including deterioration in surveillance pulmonary function test values, prompts further investigations, including bronchoscopy and lung biopsy to obtain histologic confirmation of rejection. In small children, flexible bronchoscopy is often performed under general anesthesia through a laryngeal mask. Most patients respond to steroid therapy. If rejection persists, methotrexate and/or T-cell antibody treatment is initiated (anti-thymocyte globulin, OKT3 ).

Bronchiolitis obliterans

Bronchiolitis obliterans accounts for over 40% of deaths that occur beyond 1 year after transplant [2]. It is a histologic diagnosis of lymphocytic infiltration, fibromyxoid deposits, subepithelial fibrosis, and fibrous obliteration of bronchioles, but the biopsy is an insensitive tool because the pathology is focal. Surrogate clinical criteria for the diagnosis include a decline in FEV₁ of more than 20% from the best post-transplant baseline, using predicted values to ac-
count for growth over time [51]. Bronchiolitis obliterans is considered a process of epithelial injury (from ischemia, infection, and immunologic and mechanical trauma) followed by an aberrant repair response [52]. Acute rejection (either recurrent or severe) is the most important risk factor for developing bronchiolitis obliterans [52]. The condition is treated by the augmentation of immunosuppression, but results are generally unsatisfactory [25].

Surgical complications

Airway complications

Facilitation of the early revascularization of airway anastomoses by wrapping the area in a pedicle of viable tissue has greatly reduced the catastrophic risk of airway dehiscence. Currently, airway anastomotic stenosis is more common, occurring in approximately 16% of cases. Airway patency is assessed in the early postoperative period by bronchoscopy, and significant stenoses are dilated. Recurrent airway stenoses may require stenting. Infants have a higher incidence of tracheomalacia; however, given time it usually resolves [24].

Vascular complications

Stenosis of arterial or venous anastomoses is uncommon and usually is related to a surgical technical problem. A ventilation-perfusion scan is performed postoperatively to screen for this complication. Pulmonary venous obstruction may clinically resemble lung reperfusion injury. These entities can be differentiated during cardiac catheterization, and stenoses can be treated by balloon dilation and stent placement [24].

Primary graft failure

The ischemic and reperfusion injury inherent in the process of harvesting and implanting the donor lungs can lead to significant early dysfunction of the graft [24,25]. The incidence of failure reportedly ranges from 13% to 35% [25]. Other contributing mechanisms may include factors related to the donor’s demise and subsequent medical management, duration of ischemia time, the interruption of lung lymphatics, surgical trauma to the graft, and the systemic inflammatory response elicited by CPB.

Early graft dysfunction presents as noncardiogenic pulmonary edema, with decreased lung compliance, hypoxia, and occasionally pulmonary hypertension. Support with mechanical ventilation plus positive end expiratory pressure and careful fluid management usually is successful although modalities such as ECMO and nitric oxide have been required [53].

Gastrointestinal complications

Gastrointestinal dysmotility and gastroesophageal reflux have been reported in 50% of children who have undergone lung transplant and have been attributed to thoracic vagus nerve injury during mediastinal dissection. Management
should be proactive because these patients are at risk for microaspiration, lung injury, and bronchiolitis obliterans. Gastrointestinal dysmotility also can predispose cystic fibrosis patients to distal intestinal obstruction.

**Arrhythmias**

Supraventricular arrhythmias occur in 11% of patients and usually are self-limiting. Animal studies implicate the suture lines of the left atrial patch [24,54].

**Surgical technique**

Early re-exploration of the chest was performed in 11% of cases in one series, most commonly for bleeding [25]. Phrenic nerve injury occurred in 22% of cases, more commonly affecting the right. The risk of injury was increased if the patient had previously undergone thoracotomy. Hoarseness as a result of left recurrent laryngeal nerve injury was noted in 10% of patients. Most of these nerve injuries resolved in the first several months after transplantation, but some patients required diaphragm plication because of poor respiratory function [24,25].

**Infection**

Infection is always a significant concern after lung transplantation. The graft is in direct contact with the external environment, the cough reflex is lost, and the recipient is receiving life-long immunosuppression therapy. Infections may be associated with early graft loss and the rapid development of obliterative bronchiolitis. It appears that infants are more susceptible to severe and fatal viral infections. Likewise, fungal infections, although uncommon, can be devastating [44]. Surveillance for and treatment of infections is vitally important, as is scrupulous attention to preventative measures such as active and passive immunization of selected vaccines. Prophylaxis for opportunistic infections, including those caused by *Pneumocystis carinii* and candidiasis, usually is initiated within the first 2 weeks of transplantation. Pediatric patients are more likely to be cytomegalovirus (CMV)-negative and are at higher risk of CMV infections, especially if the donor was CMV positive. Prophylactic treatment with IV ganciclovir can be administered prophylactically or preemptively, before the clinical manifestation of CMV infection [55].

**Malignancy**

The overall incidence of malignancy is 6.5% at 1 year and 8.2% at 5 years [2]. Most malignancies are of the post-transplant lymphoproliferative disorder (PTLD) type, and the incidence seems to be higher in children than in adults [56]. Primary Epstein–Barr virus (EBV) is a related risk factor. Reduction in the level of immunosuppression therapy often results in the resolution of PTLD, but re-
ducing immunosuppression increases and hastens the likelihood of bronchiolitis obliterans. Promising newer therapies include recipient EBV-specific cytotoxic T lymphocytes and rituximab, an anti-CD20 antibody.

**Other medical complications**

Many of the other medical problems encountered after transplantation are related to immunosuppression therapy. Some issues are of worthy of mention. The incidence of neurologic complications has been reported to be as high as 47% [57]. Seizures are common, perhaps because calcineurin phosphatase inhibitors cause cerebral vasoconstriction. Most seizures do not require long-term medication. Hypertension has been reported in 36% of recipients at 1 year and 71% at 5 years after transplantation. Calcineurin phosphatase inhibitors and steroids have been implicated. Diabetes has been noted in 20% of patients at 1 year and 28% of patients at 5 years. Most cases occur in cystic fibrosis patients, suggesting that pretransplantation pancreatic disease was contributory. Tacrolimus and steroids predispose to diabetes. Renal dysfunction after lung transplantation commonly manifests as renal tubular acidosis or hypomagnesemia. Renal failure in the early postoperative period usually is related to pre-existing renal dysfunction. Late renal failure is attributed to immunosuppressive therapy.

**Survival**

A recent series [25] of more than 200 pediatric transplants has reported an overall survival rate of 76% at 1 year, 64% at 3 years, and 43% at 5 years. This finding was comparable to adult data. Of the pediatric recipients, the patients who have cystic fibrosis or pulmonary vascular disease have a poorer outcome.

Another study [2] found that early graft dysfunctions accounted for 56% of pediatric deaths in the first 2 months after transplantation, and within this group, retransplantation and living-donor lobar transplant were prominent. Later in the first post-transplant year, mortality from infection increased. After 1 year, bronchiolitis obliterans was the leading cause of death (62%), followed by infection (22%) and malignancies (14%).

Death from bronchiolitis obliterans has been found to be much less common in living-donor lobe transplant recipients [58]. It is suggested that this is related to shorter graft ischemia time rather than any immunologic advantage. Interestingly, overall survival for living-donor lobe transplantation was no better than for cadaveric lung transplantation, presumably because of higher early graft failure in the former group. Recent international data report an average half-life of 3.5 years for pediatric lung transplantation. Adolescents had the lowest conditional actuarial survival (5.4 years), and infants had the longest (7.1 years) [2,59].
A single center comparison of cystic fibrosis patients has shown that children have slightly better survival rates than adults do [38]. However, higher incidences of primary viral infection, PTLD, and noncompliance with therapy (adolescents) may ultimately put these pediatric lung transplant recipients at a greater risk of death than their adult counterparts [21].

Summary and future considerations

Lung transplantation has become an accepted therapy for children who have end-stage pulmonary disease. However, compared with heart and other solid organ pediatric transplants, survival rates for pediatric lung transplantation are lower. Bronchiolitis obliterans accounts for a significant percentage of this difference. Unlike other solid organs, the lung has a large surface area that is directly exposed to the infective and immunologic challenges of the external environment. High levels of immunosuppression are generally required. The requirement for bronchial healing is unique, as is the fact that the systemic arterial supply to the graft is not routinely reattached at surgery [1].

Unfortunately, bronchiolitis obliterans is difficult to diagnose in small children and is resistant to treatment. Further limitation of graft ischemia may help diminish its incidence. Other challenges facing pediatric lung transplant centers are the scarcity of donor organs and the long-term adverse effects of immunosuppression, particularly renal toxicity [25].

Caring for lung and heart transplant children is challenging. A thorough understanding of the relevant pathophysiology is imperative for the safe anesthetic and perioperative management of these patients before, during, and after they undergo transplantation.

References


