Aspects of Anesthesia for Lung Transplantation

Paul S. Myles, MD, MBBS, MPH, FFARCSI, FANZCA

Anesthesia for lung transplantation is both a demanding and rewarding experience. Success requires teamwork, experience, knowledge of cardiorespiratory pathophysiology and its anesthetic implications, appropriate use of noninvasive and invasive monitoring, and the ability to respond quickly and effectively to life-threatening perioperative events. Specific issues include management of a patient with end-stage lung and heart disease, lung isolation and one-lung ventilation, perioperative respiratory failure, pulmonary hypertension, and acute right ventricular failure. Recent advances include greater understanding of dynamic hyperinflation (“gas-trapping”) during mechanical ventilation, perioperative use of inhaled nitric oxide and treatment of acute right ventricular failure. Successful anesthetic management leads to greater hemodynamic stability, improvement in gas exchange and a reduction in need for cardiopulmonary bypass, all of which should lead to improved patient outcome.

Copyright © 1998 by W. B. Saunders Company.

Anesthesia for lung transplantation is one of the most complicated and demanding procedures that anesthesiologists are confronted with in their practice. Issues that arise include management of a patient with end-stage lung and heart disease, lung isolation and one-lung ventilation (OLV), perioperative respiratory failure, pulmonary hypertension and right ventricular (RV) failure, pathophysiology of cardiopulmonary bypass (CPB), coagulopathy and multiple blood product transfusion, maintenance of other vital organ function (especially brain and kidneys), and postoperative pain management. Critical incidents during the procedure are common and often life-threatening; they demand rapid assessment and intervention. This can be compromised by anesthesiologist fatigue because most lung transplantation procedures take 6 to 10 hours and usually occur at night, often after a busy cardiothoracic operating schedule.

Successful management demands both knowledge and experience, and this is best optimized by concentrating clinical exposure to lung transplantation among a small number of dedicated anesthesiologists at any one institution. Although this increases individual work load, it does enhance expertise and consistency of practice. Work schedules the day after transplantation can be reorganized, and this is most efficiently achieved with a cohesive cardiothoracic anesthetic team. As with other types of specialized surgery, outcome after lung transplantation may be affected by caseload, with larger units having more favorable results. Accumulating experience within an institution is also associated with improved outcome; at the author’s institution, a 50% reduction from 20% to 10% in early (<90 days) postoperative mortality rate over the first 7 years of the program (G. Snell, personal communication, May 20, 1997) has been observed.

Ideally, clinical practice should be evidence-based, guided by clinical trials showing superiority of one treatment over another. However, it is not surprising that most areas of lung transplantation practice are not supported by controlled clinical trials, but rely on personal experience, published case reports, and case series, usually from established centers. It is not hard to understand why clinical research is very difficult to perform in patients undergoing lung transplantation. There is often a scarcity of suitable patients because of a low caseload in any particular unit, and even then, patients may not be suitable for enrollment into a clinical trial because of both ethical reasons and time constraints: the admission process and preoperative period are often rushed, with an extremely anxious patient about to undergo a life-threatening procedure. Because the procedures often take place after hours, researcher notification may be overlooked or an opportunity for enrollment...
(explanation and informed consent) may not occur. There is also a heterogeneity of recipients, as to indication for transplantation and coexistent disease, and medical care, including anesthesiology, surgical, and respiratory care.

The most common types of lung transplantation include single-lung transplantation (SLTx), bilateral sequential lung transplantation (BSLTx), and heart-lung transplantation (HLTx). Several excellent reviews have been previously published. This review focuses on some of the specific and shared aspects of each of these procedures, and also discusses the impact of recent advances in anesthesia and critical care relevant to lung transplantation.

Preoperative Evaluation

Patients undergoing lung transplantation usually have some form of end-stage lung disease and can be conveniently divided into four groups: (1) suppurative lung disease, (2) emphysema, (3) restrictive lung disease (pulmonary fibrosis), and (4) pulmonary hypertension, with or without congenital heart disease. Experience from the author's institution, in which 47 HLTx, 88 SLTx, and 82 BSLTx have been performed since 1989, is typical of those with a high caseload (Table 1). Most patients awaiting lung transplantation have undergone extensive workups to assess their clinical status and suitability for transplantation. Available information should include medical history, including details of previous thoracic surgical procedures, and results of laboratory testing: lung function (chest radiograph estimate of lung size, arterial blood gases [ABGs], spirometry, and ventilation-perfusion scan), heart function (echocardiography, catheterization, and sometimes coronary angiography), renal function (electrolyte levels and creatinine clearance), and hematology, blood group, and viral serology.

The lung transplant recipient is usually informed of the impending operation 2 to 4 hours before it is scheduled. This is often a time of conflicting emotions for the patient and family. There is a sense of relief and excitement, and yet heightened anxiety. The patient’s emotional state may also adversely affect cardiorespiratory status, with increased dyspnea, tachycardia, and hypertension. During this period, the patient presents to the hospital and is formally admitted by the surgical unit; they have repeat blood tests and chest radiograph performed, and sign a consent form. This is followed by an anesthetic assessment, which should include routine anesthetic details; in particular, fasting status and previous response to general anesthesia, airway assessment, and cardiorespiratory examination. The procedure is then briefly described to the patient, with reassurance and support, and their questions are answered. At this stage, it is then appropriate to discuss the benefits and risks of thoracic epidural anesthesia, if indicated, for which the patient is asked to provide specific verbal consent; a note of this should be made in the medical record.

Premedication routinely includes the immunosuppressant drugs azathioprine and cyclosporine, and may include an anxiolytic (eg, midazolam, 5 mg intramuscularly) and bronchodilator therapy (eg, albuterol, 500 mg, and ipratropium, 250 μg, via nebulizer). Sedative agents, such as benzodiazepines or opioids, should be used with caution in these patients because they may result in further carbon dioxide (CO2) retention and/or hypoxia, both of which may exacerbate pulmonary hypertension or result in agitation or confusion (CO2 narcosis). Supplemental oxygen may be required during transfer to the operating room for some recipients.

<table>
<thead>
<tr>
<th>Type of Preexisting Disease</th>
<th>HLTx</th>
<th>SLTx</th>
<th>BSLTx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suppurative lung disease [n = 63]</td>
<td>8</td>
<td>54</td>
<td>1</td>
</tr>
<tr>
<td>Cystic fibrosis Bronchiectasis</td>
<td>12</td>
<td>71</td>
<td></td>
</tr>
<tr>
<td>Emphysema [n = 93]</td>
<td>9</td>
<td>12</td>
<td>71</td>
</tr>
<tr>
<td>Alpha, antitrypsin deficiency Idiopathic emphysema Sarcoid</td>
<td>2</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Interstitial lung disease [n = 17]</td>
<td>3</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>Idiopathic pulmonary fibrosis Scleroderma</td>
<td>12</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Bronchiolitis obliterans Pulmonary hypertension [n = 45]</td>
<td>27</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>Primary pulmonary hypertension Congenital heart disease</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note. Fewer HLTx procedures are currently performed, in favor of increasing popularity of BSLTx.
Patient Preparation and Monitoring

On arrival in the operating room, peripheral intravenous access and patient monitoring are established. These include pulse oximetry, electrocardiography, and invasive pressure monitoring (systemic arterial, central venous, and pulmonary arterial) and, after intubation, capnography, inhalation agent, and body temperature monitoring. There have recently been descriptions of other monitoring devices that may be beneficial during lung transplantation. Continuous cardiac output measurement, mixed venous oximetry, RV ejection fraction, and transesophageal echocardiography (TEE) have their proponents for other cardiothoracic procedures and, if considered beneficial for those procedures, they probably have their greatest cost-benefit applications during lung transplantation (particularly BSLTx and HLTx). More recent innovations include continuous ABG monitoring, in which intravascular sensors can reliably measure arterial blood pH and carbon dioxide (PCO₂) and oxygen tension (PO₂) continuously through a peripheral arterial cannula. Because of the potential for significant and sometimes rapid acid-base disturbances, both during the intraoperative and postoperative periods, this device may prove to have a role during most lung transplantation procedures. Side-stream spirometry is another innovation that may reveal subtle changes in lung mechanics. Together, these monitors can lead to the early detection of endobronchial tube misplacement, fluid overload, reperfusion injury, acute allograft rejection, or such simple problems as sputum plugging or collapse by continuously monitoring alveolar-arterial P O₂ gradient and lung compliance/resistance.

Avoidance of intraoperative hypothermia is important, particularly in those patients in whom CPB is to be avoided, because hypothermia can exacerbate pulmonary hypertension, impair coagulation, and delay recovery from anesthesia. The most effective method is forced air warming, even though efficiency may be reduced because of the need to expose the groin if femoral cannulation is required for urgent CPB. Although less effective, other methods are also often used: intravenous fluid warming and a heated and humidified circuit mattress.

Table 2. Management of Acute Pulmonary Hypertension and RV Dysfunction

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Preoperative evaluation  For identification of at-risk patients</td>
</tr>
<tr>
<td>2</td>
<td>Invasive monitoring  Pulmonary artery catheter  Mixed venous oximetry  RV ejection fraction  Continuous cardiac output  Transesophageal echocardiography</td>
</tr>
<tr>
<td>3</td>
<td>Avoid pulmonary vasoconstriction  Hypoxia, hypercapnia, and acidosis  Reflex response to light anesthesia  Beware vasoconstrictor therapy</td>
</tr>
<tr>
<td>4</td>
<td>Use IV pulmonary vasodilators  Sodium nitroprusside, 0.2 to 2 µg/kg/min  Prostacyclin, 2 to 15 ng/kg/min  Also isoflurane, epidural anesthesia</td>
</tr>
<tr>
<td>5</td>
<td>Inotrope therapy  Epinephrine, 20 to 200 ng/kg/min  Dobutamine, 5 to 20 µg/kg/min  Dopamine, 5 to 20 µg/kg/min  Milrinone, 0.125 to 0.375 µg/kg/min</td>
</tr>
<tr>
<td>6</td>
<td>Inhaled nitric oxide, 20 to 40 ppm, and reduce IV pulmonary vasodilators</td>
</tr>
<tr>
<td>7</td>
<td>If unresponsive, or worsening RV dysfunction  Metaraminol, 0.5 to 2.0 mg  Norepinephrine, 20 to 200 ng/kg/min</td>
</tr>
<tr>
<td>8</td>
<td>If unresponsive, initiate CPB</td>
</tr>
</tbody>
</table>

Abbreviations: IV, intravenous; ppm, parts per million; RV, right ventricular; CPB, cardiopulmonary bypass.

Anesthesia

Specific anesthetic management for lung transplantation depends on the type of procedure performed (HLTx, SLTx, or BSLTx) and is also guided by each institution’s (or anesthesiologist’s) nontransplantation cardiothoracic anesthetic practice. There are several critical stages in which the anesthesiologist must be particularly vigilant and remain responsive to life-threatening critical incidents. These are induction of anesthesia, commencement of positive-pressure ventilation, institution of OLV, pulmonary artery (PA) clamping, PA unclamping, and reperfusion of the lung allograft. Each of these critical stages are discussed in detail.

Induction of Anesthesia

Preoxygenation should precede induction of anesthesia. Because alveolar denitrogenation is slowed by impaired ventilation-perfusion matching, this will require a longer time period. This process can be conveniently monitored by end-
tidal oxygraphy, if available, in which induction of anesthesia is delayed until end-tidal oxygen exceeds 85% to 90%. For similar reasons, wash-in of the inhalation agent may take considerably longer than normal during the early phase of anesthesia; therefore, patients remain at risk of awareness unless adequate alveolar concentrations are achieved, which again are most reliably documented with end-tidal inhalation agent monitoring.

Induction of anesthesia and initiation of mechanical ventilation may result in significant hypotension because of the vasodilating and myocardial depressant properties of the anesthetic agents (predominantly left ventricular [LV] dysfunction), as well as increases in intrathoracic pressure and pulmonary vascular resistance (PVR) (predominantly RV dysfunction). These issues are described below. Most lung transplant recipients have normal myocardial function and slightly elevated PA pressure, although they often have increased potential for acute increases in PVR because of pulmonary vascular medial wall hypertrophy. A carefully titrated induction of anesthesia using any of the induction agents is suitable for most patients, provided there is meticulous observation and maintenance of systemic and PA pressures. This is usually supported by preemptive intravascular volume loading, which maintains ventricular preload.

In patients with impaired ventricular function or greater degrees of pulmonary hypertension, most notably those with primary pulmonary hypertension or cyanotic congenital heart disease, induction of anesthesia needs to be further modified. These patients are at increased risk of profound hypotension and circulatory arrest. A carefully titrated induction of anesthesia using any of the induction agents is suitable for most patients, provided there is meticulous observation and maintenance of systemic and PA pressures. This is usually supported by preemptive intravascular volume loading, which maintains ventricular preload.

The airway should be secured rapidly after the induction of anesthesia because these patients are often difficult to ventilate adequately using a bag and mask (because of the need for higher inflation pressures), and many are at risk of pulmonary aspiration. This is best achieved by using succinylcholine, 1.5 mg/kg, or more recently, rocuronium, 0.6 to 1.0 mg/kg. For patients undergoing SLTx and most of those undergoing BSLTx, a method of lung isolation is required. The most common device is a disposable polyvinylchloride or reusable red rubber double-lumen tube, although the Univent tube (Fuji Systems; Tokyo, Japan) or bronchial blocker is occasionally used. Endobronchial tube position should then be checked with fiberoptic bronchoscopy to ensure optimal position; this can also aid aspiration of airway secretions in those patients with suppurative lung disease. There are occasions when lung ventilation may be impaired or lung isolation compromised; this requires vigilance and manipulation of the endobronchial device. Because HLTx and some BSLTx are performed using CPB, a standard endotracheal tube can be inserted for these cases. It may also be appropriate to use a double-lumen tube in some BSLTx cases in which CPB is planned (during the dissection phase) to reduce CPB time.

Initially, an inspired oxygen fraction ($F_{O_2}$) of 1.0 is chosen, but this may be reduced in some
patients if tolerated, even during OLV. This is because a high \( F_02 \) is thought to increase the risk of lung injury, although this becomes more relevant after lung allograft implantation.\(^{50,51}\) In those patients at risk of dynamic hyperinflation (DHI), it is preferable to maintain a high \( F_02 \) because hypoventilation or periods of apnea may be required (information to follow). Although used occasionally in some units, \( N_2O \) is best avoided during lung transplantation because it can increase PVR.\(^{52}\)

Maintenance of anesthesia varies according to the type of operation and underlying disease status. Because most transplant recipients are not particularly at risk of myocardial depression, standard concentrations of volatile agents (most commonly isoflurane, which promotes bronchodilation and pulmonary vasodilation)\(^{53}\) or intravenous anesthesia (eg, propofol infusion, 3 to 5 mg/kg/hr) can be used. High-dose opioid techniques have also been described,\(^{17,19}\) but this delays recovery and eventual extubation. A high-dose opioid technique may be more suitable for patients undergoing HLTx, or BSLTx with CPB, particularly if their underlying disease suggests a complicated postoperative course in which early extubation is not anticipated. Patients with congenital heart disease and pulmonary hypertension, particularly if they have undergone previous thoracic surgery and have a greater blood loss expected, are often electively ventilated beyond 12 to 24 hours.\(^{4,54}\)

Although most patients have normal LV function, there are critical times throughout the procedure when episodes of severe hypotension can occur (see below). In these situations, it is usual to reduce the depth of anesthesia and this may result in awareness.\(^{55}\) This risk can be reduced by concomitant use of benzodiazepines. For this reason, adjunctive agents such as potent opioids or midazolam are used for all lung transplantation procedures.

**Mechanical Ventilation**

Although positive-pressure ventilation enables gas exchange during lung transplantation, it is associated with many complications.\(^{9,11,20,56,57}\) High airway pressure has direct and indirect adverse effects. It can directly lead to barotrauma (pneumothorax, mediastinal emphysema, air leak through a tracheal/bronchial anastomosis) or indirectly by volutrauma (lung hyperinflation and circulatory collapse).\(^{58}\) The risk for these complications is in part dependent on the ventilator settings chosen and these are determined by the patient’s status and the desired arterial PO\(_2\) and PCO\(_2\) values.\(^{20,30-63}\) The standard normal values of PO\(_2\) (100 mmHg) and PCO\(_2\) (40 mmHg) are often inappropriate in this population because the patient may have adapted to levels outside the normal range. The best guide to an acceptable ABG value for an individual patient is the preoperative value. Higher levels of PCO\(_2\) can often be tolerated and this realization has led to the concept of “permissive hypercapnia.”\(^{4,5,10,20,64}\) By allowing a reduction in minute ventilation, acceptance of permissive hypercapnia reduces the adverse effects of mechanical ventilation. Levels of PCO\(_2\) as high as 60 mmHg are commonly accepted and levels as high as 120 mmHg have been reported without adverse sequelae,\(^{1,11,20}\) although it should be remembered that hypercapnia can exacerbate pulmonary hypertension.\(^{65,66}\)

Patients with severe airflow obstruction (asthma, cystic fibrosis, and emphysema) are at risk for DHI, or gas-trapping, during positive-pressure ventilation (Fig 1).\(^{9,11,20,61}\) DHI results in residual positive end-expiratory pressure (PEEP) and so is also known as auto-PEEP or intrinsic PEEP.\(^{56,61,67,68}\) This results in overinflation of the lungs, reduction in venous return, and direct compression of the heart. The resultant tamponade effect can lead to severe hypotension, and even cardiac arrest.\(^{9,11,20,61}\) Lesser degrees of this are very common during lung transplantation, particularly early after induction when there is a tendency to hyperventilate the lungs at the same time that anesthetic drug-induced myocardial depression and vasodilation occur. In general, PEEP is not recommended in patients with severe airflow obstruction, although there is some evidence that if extrinsically applied PEEP is less than intrinsic PEEP, DHI will not be aggravated.\(^{69}\) The most important aspect is to remain aware of the possibility of DHI and maximize expiratory time so that the lungs have time to empty before the next inspiratory cycle begins. If hypotension remains troublesome, then a period of circuit disconnection (apnea) should resolve the situation.\(^{9,20}\)

An alternative mode of ventilation is high-frequency jet ventilation (HFJV), which operates at lower peak airway pressure and so, theoreti-
Figure 1. Reduction in dynamic hyperinflation (volume of trapped gas) with maximized expiratory time. Abbreviation: FRC, functional residual capacity. (Adapted and reprinted with permission from Myles PS, Ryder IG, Weeks AM: Diagnosis and management of dynamic hyperinflation during lung transplantation. Cardiothorac Vasc Anesth 111:100-104, 1997.)

HFJV is useful in patients with bronchopleural fistula and giant bullae. Conacher has reported success with a modified form of HFJV in patients at risk for DHI, predominantly lung transplant recipients, using prolonged expiratory pauses to assist lung emptying. However, a recent clinical trial failed to show the superiority of HFJV when compared with conventional intermittent positive-pressure ventilation that included the above recommended ventilator settings (“optimal” intermittent positive-pressure ventilation).

Patients with pulmonary fibrosis can usually be ventilated with a normal respiratory pattern and may gain added benefit from PEEP. Because positive-pressure ventilation also increases PVR, patients with primary or secondary pulmonary hypertension may initially be adversely affected early after induction. However, correction of hypoxia and hypercapnia may ultimately result in better hemodynamic control. The extent to which PEEP is transmitted to the circulation (by increasing PVR and reducing ventricular filling) is dictated by the underlying lung disease. Patients with interstitial lung disease (low lung compliance) are less likely to transmit intrapulmonary pressure compared with those with emphysematous lung disease (high lung compliance). The anesthesiologist can also obtain information from the changes in arterial pressure during the respiratory cycle, particularly by observing systolic pressure variation.

Further clarification of the beneficial or adverse effects of PEEP on a particular patient can be obtained by measuring mixed venous and ABGs, cardiac output, systemic and PA pressure, oxygen delivery, and derived indices of preload and afterload.

One-Lung Ventilation
Initiation of OLV is another challenging event because, by definition, these patients often have borderline oxygenation during two-lung ventilation. For most patients, the sooner the hilum of the lung can be dissected and the pulmonary artery ligated, the better (most surgeons ligate each branch of the pulmonary artery as they proceed). This enhances pulmonary blood flow to the ventilated lung and also blunts the acute changes in PVR. Some patients cannot tolerate OLV and CPB is required. Several groups have attempted to identify these patients preoperatively, so that they may be electively managed on CPB (either because of profound hypoxia or unacceptably elevation in PA pressure and acute RV failure). Use of these criteria has not been validated, or widely accepted. The most logical management plan is to optimize lung ventilation and hemodynamics, and only proceed to CPB if the patient remains unstable or if surgical access is compromised. Maneuvers to improve oxygenation during OLV include all of those used during nontransplantation thoracic surgery, such as intermittent lung inflation (perhaps the
most effective maneuver), providing continuous positive airway pressure to the nonventilated lung, or providing PEEP to the ventilated lung, with the previously mentioned restrictions. Hypoxia during OLV appears to be less of a problem in patients with emphysema. 80,81

Clamping of the Pulmonary Artery

Patients with end-stage lung disease often have some degree of secondary pulmonary hypertension and RV hypertrophy, and are at risk of acute elevations of PVR and RV failure. 1,3,4,6,17 The ultimate condition, however, is primary pulmonary hypertension, in which hypoxia, hypercapnia, arrhythmias (even tachycardia), and systemic hypotension may all precipitate RV failure. 19 Most of these high-risk patients undergo HLTx or BSLTx and require CPB. 1,2,7,29,30,44 These patients, and those with more advanced secondary pulmonary hypertension, have a complex relationship between right and left ventricles, known as ventricular interaction, ventricular interference, or interventricular dependence (Fig 2). 42,45,82,83 Acute RV failure results in dilatation and bulging of the ventricular septum toward the LV in these patients. This reduces LV filling and impairs contractile function. A vicious circle then develops, resulting in worsening RV function and ultimately cardiac arrest. Appreciation of this concept and how it can be circumvented is crucial for anesthesiologists involved in both lung and heart transplantation.

These principles include identification of those at risk, vigilance, invasive monitoring, maintenance of intravascular volume and myocardial contractility, and judicious use of vasoactive agents.

Figure 2. The effect of ventricular interaction. An acute increase in pulmonary artery pressure may result in acute RV failure, leading to RV dilatation, septal shift toward the left ventricle, and LV failure. This situation may become irreversible, particularly if coronary blood flow to the RV is compromised by increasing RV wall tension and worsening hypotension. Abbreviations: PA, pulmonary artery; IPPV, intermittent positive-pressure ventilation; PEEP, positive end-expiratory pressure; CVP, central venous pressure.
Acute increases in PVR occur after induction of anesthesia, initiation of OLV, and most dramatically, during PA clamping and ligation. At each of these times, pulmonary hypertension will be made worse by hypoxia, hypercapnia, and metabolic acidosis. The anesthesiologist should monitor PA and central venous pressure and directly observe RV function through the surgical incision (and/or communicate with the surgeon). Other monitoring may be of assistance (TEE, continuous cardiac output, RV ejection fraction, mixed venous oximetry, ABGs).

RV function can be improved with inotrope therapy (eg, epinephrine, 20 to 200 ng/kg/min) and reduction in PVR using a pulmonary vasodilator (eg, sodium nitroprusside, 0.2 to 1.0 μg/kg/min, or prostacyclin, 2 to 10 ng/kg/min). Alternatively, a milrinone infusion, 0.125 to 0.375 μg/kg/min, may be used. Fluid loading should be used cautiously, because RV function may deteriorate rapidly. This regimen is usually successful in those patients with moderate elevations in PVR, but care should be exercised in those with more severe pulmonary hypertension and RV failure. Unfortunately, all currently available intravenous pulmonary vasodilators can result in unacceptable systemic hypotension, necessitating a reduction in infusion rate and possibly a concomitant increase in inotropic requirement, which may actually increase PVR. In these cases, the most reliable method of avoiding what may become an irretrievable situation is to treat systemic hypertension with a vasoconstrictor (eg, norepinephrine). Administration of a vasoconstrictor through a left atrial catheter has also been described, aiming to bypass the pulmonary circulation and reduce PVR, although a recent double-blind trial failed to show any benefit with this technique early after heart transplantation. Mild-to-moderate elevations in PVR are usually best treated initially with a vasodilator, and more severe elevations in PVR, especially if associated with acute RV dysfunction, are best treated with a vasoconstrictor (eg, norepinephrine).

A highly selective pulmonary vasodilator, inhaled NO, is now available in most institutions. At a dose of 20 to 40 ppm, inhaled NO reduces PVR and reverses RV failure, leading to improved cardiac output. Lower doses (1 to 5 ppm) can also be used in patients with severe adult respiratory disease to improve oxygenation and reduce PVR. Myles and Venema were able to reverse an acute deterioration during BSLTx and avoid CPB using NO at 40 ppm. Early NO administration may also reduce reperfusion injury and be used to treat early graft dysfunction after lung transplantation. Inhaled NO therapy does not result in systemic hypotension and usually allows a reduction in inotrope requirement. This is an extremely useful addition to the armamentarium because it allows concomitant use of systemic vasoconstrictors (if required), maintaining RV and vital organ perfusion. Although the benefits appear compelling, current evidence remains anecdotal and controlled clinical trials are required to further define the role of NO in lung transplantation.

Unclamping of the Pulmonary Artery

After completion of the anastomoses, de-airing and unclamping of the pulmonary artery may also lead to profound hypotension. This has several possible causes, all of which may occur simultaneously. They include coronary artery air embolism (particularly to the right coronary artery because of its superior anatomic location), systemic release of residual allograft pneu-moplegia (which also contains prostacyclin delivered during the lung procurement), and, perhaps, release of various substrates and cytokines generated during reperfusion. It is not uncommon to observe ST-segment depression on electrocardiograph, which is suggestive of myocardial ischemia, even in those with docu-
mented normal coronary arteries. Hence, hypotension may be secondary to both systemic vasodilation and RV dysfunction, and once again is best treated with a vasoconstrictor, such as incremen
tal metaraminol (or phenylephrine) or a norepinephrine infusion. The initial dose re
duced to treat hypotension at this stage may be very high (eg, norepinephrine, 100 to 2,000 ng/kg/min), but this usually reduces rapidly, over 5 to 15 minutes. Prolonged hypotension suggests other problems, such as allograft dysfunction leading to persistent hypoxia, hypercapnia, elevated PVR, and RV failure. The allograft anastomoses (bronchial, by fiberoptic bronchos
copy; pulmonary vascular, by the surgeon) should be checked. If there is doubt about any of these, then they should be refashioned. In particular, if there is pulmonary venous obstruction from a potentially kinked anastomosis, this may lead to pulmonary edema formation and hypoxia (surgical retraction of the heart or an atrial clamp can transiently cause the same problem). Hemodynamic support may require systemic vasoconstric
tion, inotropes, and/or inhaled NO. Correction of hypoxia, hypercapnia, and acid-base status (using a slow infusion of 8.4% bicarbonate) may be useful. Reinstitution of two-lung ventilation may further relieve the situation, as PVR reduces and gas exchange improves.

Should PEEP be used after lung allograft implantation and re-expansion? Low levels of PEEP are commonly prescribed as part of the ventilator management of most critically ill patients because it promotes alveolar recruitment (impedes alveolar collapse) and so enables a reduction in F\textsubscript{O\textsubscript{2}}. The resultant increase in lung compliance also leads to a reduction in intra-alveolar pressure, and so reduces another possible cause of lung injury. For these reasons, prophylactic PEEP has been used by some enthusiasts in the intensive care unit (ICU), although there is very little evidence to support this practice. Nevertheless, many ICUs use low levels of PEEP after lung implantation. This is not an unreasonable practice, because the new lung allograft is devoid of lymphatic drainage and is also at risk of re-expansion pulmonary edema and reperfusion injury. Because of these reasons, PEEP may not be suitable in patients with emphysema undergoing SLTx after re-establishment of two-lung ventilation, because the newly implanted lung allograft has a much lower compliance than the native lung and this often results in asymmetric distribution of tidal volume, leading to native lung hyperinflation, mediastinal shift, and circulatory collapse. This problem can only be reduced using the ventilator management described for DHI. Unfortunately, increased inspiratory flow rates result in high inspiratory airway pressure, which may be detrimental to the new lung and also result in air leak through the bronchial anastomosis. In patients in whom this is problematic, it is preferable to continue lung isolation and use differential lung ventilation. The native lung is ventilated as previously described, maximizing expiratory time, and the lung allograft is ventilated with reduced F\textsubscript{O\textsubscript{2}} and low levels of PEEP. This obviously requires two ventilators and may need to be continued for some time postoperatively.

Avoiding Cardiopulmonary Bypass

CPB is used for all patients undergoing HLTx. Some institutions routinely use CPB for patients undergoing BSLTx, either generally or selectively. The benefits of CPB include avoidance of OLV and the hemodynamic effects of PA clamping, as well as improved surgical access. Patients may be exposed to fewer episodes of pulmonary hypertension, DHI, high inflation pressure (leading to air leak, lung injury, and barotrauma), hypothermia, hypoxia, hypercapnia, and acid-base disturbances. However, they are at increased risk of coagulopathy, leading to excessive postoperative bleeding and blood transfusion, as well as a greater positive fluid balance (and pulmonary edema). There is some evidence that outcome may be improved if CPB can be avoided, although if the recipient is grossly unstable during the procedure then CPB should be considered. Guidelines for emergency institution of CPB during lung transplantation have been published, although the most important consideration should be the patient’s response to interventions. Because no controlled clinical trials have yet been performed in this area, confident conclusions cannot be made.

Although most SLTx and BSLTx patients can undergo their procedure without CPB, they remain at risk of hypoxia, hypercapnia, hypotension, and arrhythmias during the various stages,
as previously described. Deterioration in gas exchange and circulatory status unresponsive to conventional therapy demands urgent CPB. Surgical access may also be compromised by lung tissue, adhesions, or small thoracic cavity size, particularly during BSLTx, and CPB may be requested. Poor allograft function after implantation of the first lung during BSLTx may require CPB for implantation of the remaining lung. In the author’s institution, it has been found that, with growing experience, the requirement for CPB has significantly decreased to less than 20% of BSLTx cases, and is rarely required for SLTx. For patients undergoing BSLTx, the lung with the lowest perfusion should generally be replaced first because this minimizes pulmonary hypertension and impaired gas exchange, and may reduce the need for CPB. In general, patients with severe pulmonary hypertension with or without congenital heart disease usually require CPB, whereas those with suppurative lung disease, restrictive lung disease, or emphysema do not. To avoid the problems associated with CPB and also avoid hemodynamic compromise during the procedure, several attempts at predicting the need for CPB have been described. Although useful as a guide, these criteria have not been validated, particularly in recent practice; (before inhaled NO was available, DHI was well described and the benefits of permissive hypercapnia were recognized). The need for CPB also depends on the experience and skills of the surgical and anesthetic teams.

Epidural Anesthesia

In patients undergoing SLTx, an extensive thoracotomy incision is performed at the level of the fifth or sixth intercostal space, with adjacent rib resection. Most of those undergoing BSLTx have a clamshell incision extending horizontally across both thoracic cavities at the lower end of the sternum. Both these incisions result in significant postoperative pain, which may impair ventilation and cough. Use of postoperative opioids will further impair respiratory function and aggravate CO₂ retention, and thus ventilator weaning and extubation can be delayed. For this reason, postoperative epidural analgesia is frequently provided for these patients. An epidural catheter can be inserted either before or after the procedure. The benefits of insertion pre-admission include confirmation of correct placement, including patient feedback if neural tissue is traumatized; reduction of general anesthetic requirements; and preemptive analgesia, whereas if the catheter is inserted at the end of the procedure, these benefits are lost and there may be greater risk of epidural hematoma if a coagulopathy is present.

A suggested regimen is to use either a combination of fentanyl, 1.5 µg/kg, and bupivacaine 0.5%, 3 to 5 mL, or fentanyl alone (until the completion of the procedure). These dosages are usually repeated every 1 to 3 hours throughout the procedure, as tolerated. A commonly used postoperative infusion regimen is an opioid/local anesthetic combination of fentanyl, 2 µg/mL, and 0.125% bupivacaine, 4 to 12 mL/hr.

One of the major concerns with thoracic epidural anesthesia is the risk of epidural hematoma because most patients are given heparin intraoperatively (routinely 5,000 units before clamping each PA, or full heparinization if CPB is required). Nevertheless, epidural anesthesia is considered safe, and the benefits of improved postoperative analgesia (facilitating earlier extubation) are persuasive. Intraoperative epidural local anesthesia can also lead to increased hemodynamic instability. Although epidural techniques can reduce general anesthetic requirements, and perhaps reduce the risk of intraoperative awareness, the potential for hypotension and ultimately a further reduction in depth of anesthesia may be counterproductive. Restricting intraoperative epidural use to opioids alone is probably the best compromise in most cases, with mixed opioid-local anesthetic epidural infusion used postoperatively to provide analgesia. Despite these concerns, there are possible benefits of mixed opioid-local anesthetic epidural infusions used intraoperatively. A reduction in general anesthetic requirements, increased pulmonary vasodilation, and a possible reduction in neurohumoral stress response leading to improvement in outcome may tip the balance in their favor. The optimal epidural drug combination for lung transplantation is yet to be determined.

Anesthesia for HLTx

The incidence of HLTx has decreased over recent years, with most patients now being man-
aged with BSLTx, with the advantages of avoiding concomitant heart transplantation and in most cases avoiding CPB. Nevertheless, there are still occasional patients requiring HLTx, most commonly those with primary pulmonary hypertension or those with end-stage lung disease and coexistent heart disease. These patients are usually high risk, with most having significant pulmonary hypertension and RV dysfunction, and have often had previous heart surgery. Anesthetic management should include those measures that avoid increased PVR and maintain myocardial contractility, as previously discussed. Measures to reduce perioperative bleeding (antifibrinolytics) and blood transfusion (cell-saving) are often indicated (information to follow).

### Fluid Management and Blood Transfusion

Lung transplantation, especially HLTx and BSLTx, can be a prolonged procedure producing significant blood loss and requiring large amounts of fluid administration. This is particularly so if previous thoracic surgery has occurred (with multiple, often vascular, pleural adhesions) or if CPB is required. The lung allograft is at increased risk of pulmonary edema (absence of lymphatic drainage, re-expansion pulmonary edema, and reperfusion injury). The best fluid management regimen is uncertain but it appears logical to avoid excessive crystalloid administration and favor fluid restriction. Because of this, hypotension may be problematic and judicious use of a vasoconstrictor and/or an inotrope is required. Patients undergoing lung transplantation with CPB generally have a larger positive fluid balance, leading to pulmonary edema and impaired gas exchange. In contrast, there are some situations in which, for technical reasons, pulmonary venous drainage can be improved by stopping mechanical ventilation and completing the implantation with CPB. This may or may not reduce pulmonary edema and improve postoperative lung function.

The need for blood transfusion is dictated by the patient's preoperative hematocrit (often high in this population) and the intraoperative course. Regular measurement of the hematocrit (and perhaps cardiac output and oxygen delivery) can guide rational fluid administration. If indicated, fresh frozen plasma and platelet transfusion may also be required. Autologous transfusion can be reduced with a cell-saver device, and this is particularly useful in those patients who have extensive vascular adhesions (history of previous thoracic surgery, pleurodesis, or recurrent pleurisy). In these cases, early administration of an antifibrinolytic agent (e-aminocaproic acid, tranexamic acid, or aprotinin) may also be helpful.

### Other Drug Therapy

Patients undergoing lung transplantation often receive a large number of anesthetic and vasoactive drugs. It is important not to overlook the intraoperative requirement for immunosuppressants: methylprednisolone, 500 mg, is given at induction of anesthesia and a second dose is given during allograft reperfusion.

At the author's institution, routine antibiotic therapy consists of cephalothin, 2 g, at induction, and then 1 g every 6 hours for 24 hours postoperatively. Patients with infective lung disease (cystic fibrosis and bronchiectasis) require individualization of antibiotic administration to cover resistant organisms such as *Pseudomonas* and multidrug resistant *Enterococci* and *Staphylococci*. Some recipients may have been recently hospitalized for respiratory failure and so may harbor resistant organisms as well. For all antibiotics, repeated dosing may be required intraoperatively and this should not be overlooked.

Many patients undergoing lung transplantation have a reversible component to their obstructive airways disease, and so preoperative bronchodilator therapy should be continued intraoperatively. This will reduce the risk of hypoxia, hypercapnia, and DHI, and may reduce the need for CPB.

### Assessment of Functional Result

Successful allograft implantation and lung function can be assessed almost immediately. The airway anastomoses can be checked with fiberoptic bronchoscopy and the lung should appear pink after reperfusion. There should be a dramatic reduction in PA pressures, often with an improvement in RV function, after unclamping and hemodynamic stabilization. There should
also be improvements in CO₂ clearance and oxygenation, allowing reductions in F₁O₂ and minute ventilation. A reduction in airway pressure is common. Further objective assessments can also be made. Both the arterial end-tidal CO₂ gradient (an indicator of alveolar deadspace) and the alveolar-arterial O₂ gradient (an indicator of gas transfer and ventilation-perfusion matching) should decline.³,³⁹ Lung mechanics (compliance and resistance) can also be measured using side-stream spirometry.

**Postoperative Care**

Stabilization in the ICU is the immediate goal, along with early assessment of lung function, using the previously described methods, as well as chest radiograph, repeated bronchoscopy, and lung biopsy. With recovery from anesthesia and achievement of normothermia, extubation can occur. This is assisted by reduced intraoperative opioid administration, avoidance of CPB, and effective postoperative analgesia.¹

Significant postoperative complications include lung infection and/or rejection (both leading to respiratory failure and prolonged mechanical ventilation), hemorrhage, neurologic injury (brain, phrenic nerve, brachial plexus), drug toxicity (immunosuppressants, antibiotics, sedatives), and muscle weakness (myopathy, neuropathy, malnutrition).⁵,⁸,¹²,⁵⁴,⁹⁵,¹¹⁴-¹²⁰

Optimization of analgesia should continue throughout the postoperative period. Ongoing contact with the patient and their family can provide reassurance and allow opportunity for further questions regarding their intraoperative course and postoperative progress. This also provides feedback to the anesthesiologist about their perioperative management and performance and is a good opportunity to inquire about intraoperative awareness.

**Conclusion**

Anesthesia for all types of lung transplantation is both a demanding and rewarding experience. Success requires teamwork, experience, knowledge of cardiorespiratory pathophysiology and its anesthetic implications, vigilance (with clinical assessment, noninvasive and invasive monitoring), and the ability to respond quickly and effectively to life-threatening perioperative events.

Advances in lung transplantation await the benefits gained from further experience and ongoing medical research.

**Acknowledgment**

The author thanks Drs Tony Weeks, Mark Buckland, and Michael Bujor, for their constructive comments on this article and their dedicated teamwork approach for heart and lung transplantation within the department, and Dr Greg Snell for providing some of the patient data in this report, and acknowledge Don Esmore and all members of the Heart and Lung Replacement Service for their expert clinical care.

**References**

13. Globis S, Burbuber OC, Koller J: Effect of lung transplantation on right and left ventricular function mea-
41. Stoelting RK, Longnecker DE: Effect of right-to-left shunt on rate of increase in arterial anesthetic concentration. Anesthesiology 36:352-356, 1972
50. Davis WB, Rennard SI, Bitterman PB: Pulmonary oxygen toxicity. Early reversible changes in human alveolar...
86. Ghignone M, Girling L, Prewitt RM: Volume expansion versus norepinephrine in treatment of a low cardiac output complicating an acute increase in right ventricular afterload in dogs. Anesthesiology 60:132-135, 1984
104. Myles PS, Leong CK, Weeks AM: Early hemodynamic
effects of left atrial administration of epinephrine after heart transplantation. Anesth Analg 84:976-981, 1997