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Anesthetic implications for lung transplantation

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Lung transplantation (LT) is the only therapy currently available for end-stage pulmonary disease involving destruction of lung parenchyma and vasculature. It is reserved for patients who have failed maximal medical therapy (eg, newer antibiotic regimens in cystic fibrosis patients and prostacyclin therapy in patients with pulmonary hypertension) but who are still able to care for themselves. By the end of 2002, a record number of patients (3756) were registered for LTs [1]. This number reflects a 300% increase in the number of patients waiting for transplantation since 1993. The number of these patients older than 50 years of age has increased from approximately 35% in 1993 to over 50% in 2003 [1]. After a modest increase in the number of US lung transplants since 1993, the total number of LT has remained at approximately 1000 per year for the past 5 years (Fig. 1). This plateau has been ascribed to a relatively stable number of donor candidates [2] and an increased number of double-lung transplants over the past several years [1]. This leveling of the annual rate of lung transplants has resulted in a doubling of median waiting times to approximately 1.5 years [1] and an increased number of patients dying while waiting for a lung transplant. Currently there are almost 90 centers performing LT in the United States, but only a third of these programs perform more than 10 LT procedures per year [2]. The unadjusted

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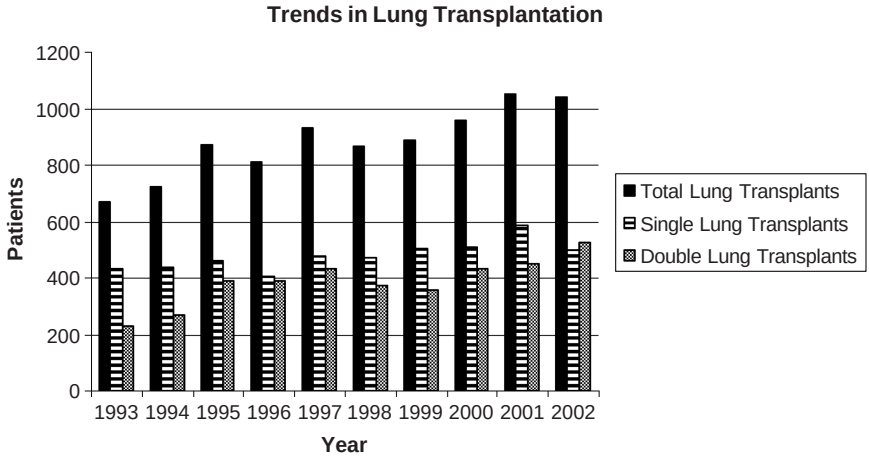

Fig. 1. The total number of LTs have reached a plateau at approximately 1000 per year. Double-LTs have increased 40% since 1999. (*Data from* 2003 OPTN/SRTR Annual Report 1993–2002. HHS/HRSA/OSP/DOT; UNOS/URREA. The data and analyses reported in the 2003 Annual Report of the US Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients have been supplied by UNOS and URREA under contract with HHS. The authors alone are responsible for reporting and interpreting these data.)

1- and 5-year mortality rates for all lung transplant recipients are 78% and 45%, respectively [1]. It is assumed by some that low volume programs will have inferior results [3].

Indications and recipient and donor characteristics

Since LT became technically successful in the 1980s, the spectrum of diseases for which transplantation can be offered has expanded greatly (Box 1). Chronic obstructive pulmonary diseases (primarily emphysema and α_1-antitrypsin deficiency) are the most common indications for LT followed by cystic fibrosis [1,4]. LT has been documented as a viable option for lung cancer, especially bronchoalveolar carcinoma [5]. Potential recipients are strongly encouraged to maintain a healthy lifestyle, discontinue smoking, and improve physical conditioning while awaiting transplantation.

Criteria for recipients have been relaxed significantly since the first operations in the 1960s. Currently, the age limit is 55 years old for heart-lung transplant recipients, 60 for bilateral-lung transplant recipients, and 65 for single-lung transplant recipients [6]. Contraindications to LT have evolved over the years as medical therapy has improved (Box 2) [7,8]. For example, it is now common for patients receiving moderate doses of corticosteroids to undergo transplantation. At the extreme, some patients, such as those with severe pulmonary hypertension, have been put on extracorporeal membrane oxygenation (ECMO) before

Box 1. Indications for lung transplantation

Single-LT

- Emphysema (forced expiratory volume $[FEV]_1$, $\leq$ 25% predicted), tobacco use, α_1-antitrypsin deficiency
- Pulmonary fibrosis
- Pulmonary hypertension (mean pulmonary arterial pressure $\geq$ 55 mm Hg)
- Connective tissue disorders: sarcoidosis, eosinophilic granulomas, lymphangioleiomyomatosis
- Interstitial lung disease: chemotherapy, radiation therapy
- Bronchoalveolar carcinoma (controversial)

Double-LT

- Septic pulmonary disease ($FEV_1 \leq$ 30% predicted): cystic fibrosis, bronchiectasis
- Pulmonary hypertension
- Emphysema

undergoing LT [9] because of the fear of catastrophic complications during the induction of anesthesia.

Allocation of donor lungs is based primarily on recipient waiting time as opposed to severity of illness criteria used in other solid organ transplants [10]. Because donor lungs are especially susceptible to infection, previous inflammatory injury, and ischemia, fewer than 20% of cadaveric donors have lungs suitable for harvest [1]. This generally precludes HLA typing and limits the geographic distribution for donor lungs. Instead, donor lungs are matched to the recipient based solely on gross anatomic size and primary blood group typing. Generally, donors are less than 60 years of age and have minimal smoking histories, but liberalization of these policies has been reported [11–13]. Once accepted, donor lungs are harvested through a median sternotomy and maintained in cold preservative solution. The lungs are expanded and packed in an iced preservative solution for transport.

Ischemic time of the donor lung is an important issue that has been shown to correlate inversely with success of the transplant operation, an effect most pronounced after 5 hours of ischemia [7]. This underscores the importance of logistical planning and close communication between the entire surgical and medical staffs for both the donor and recipient for synchronizing the harvest with initial preoperative preparation and intraoperative anesthetic management. To minimize delays at the authors' institution, once the harvesting team determines that the lungs are likely to be suitable, recipients are admitted to the intensive care

Box 2. Contraindications to lung transplantation

Absolute Contraindications

- Ventilator dependence
- Incurable malignancy
- Concurrent serious medical illness
- Chronic incurable infection: HIV, hepatitis, pan-resistant bacteria
- Obesity or cachexia
- Psychosocial difficulties: tobacco use, mental illness, substance abuse
- Severe chest wall deformity or pleural disease

Relative Contraindications

- Age: $\geq$ 65 years for single-lung transplant, $\geq$ 60 years for double-lung transplant
- Previous thoracic surgery
- Severe peripheral vascular disease
- Corticosteroid dependence

Adapted from DeMeo DL, Ginns LC. Clinical status of lung transplantation. Transplantation 2001;72(11):1713–24.

unit (ICU) or the operating room holding area to have appropriate central lines and a thoracic epidural placed. Occasionally, however, the recovery team determines that the donor lungs are unsuitable only after direct physical examination, which necessitates canceling the operation. This can occur after the recipient is anesthetized. Frank discussions of these technical issues with the patient and family are an important part of the preoperative evaluation.

Anesthetic considerations: preoperative evaluation and preparation

Patients presenting for LT may have been on a waiting list for months to years, and interval changes in health status are likely to have occurred. Fortunately, adequate time is usually available to evaluate the medical records and the results of recent studies, especially recent cardiopulmonary function studies such as echocardiograms, pulmonary function tests, and radionuclide scans. It is also crucial to ascertain the baseline functional status of the recipient. Acute deterioration in exercise capacity or new symptoms at rest is findings that must be investigated. Close physical examination of the airway, heart, and lungs is critical.

After performing a careful history and physical, the anesthesiologist is usually responsible for placing intravenous catheters and invasive monitors. If possible, one or preferably two large-bore (14 or 16 gauge) peripheral intravenous catheters should be inserted. Because there is some likelihood that any lung transplant operation may necessitate the use of cardiopulmonary bypass (CPB), the authors place pulmonary artery catheters through the right internal jugular vein. Unless CPB is a very likely possibility (pulmonary artery pressures acutely elevated, $\geq$55 mm Hg, with right heart failure), thoracic epidural catheters (T6–T8) are also placed before induction. The authors have found the paramedian approach to be the easiest in this region and almost always place the epidural catheter with the patient in the sitting position.

Two important points must be made regarding placement of these lines and catheters. First, as in all patients but especially in patients soon to begin immunosuppressive therapy, meticulous sterile technique must be followed. Second, these patients are often anxious, and line placement is painful; premedication with anxiolytics and analgesics is often necessary. Many lung transplant recipients, however, are hypercapnic and depend on their hypoxic drive to breathe, so close observation of respiratory status is needed. Supplemental oxygen is used for most of these patients with special care to use minimum nasal cannula flow rates of 1–2 L/min. Sedation can also produce hypotension by decreasing the effect of circulating catecholamines [14]. Administering midazolam is favored, 0.5–1 mg intravenous (IV), and fentanyl, 25–50 μg, although many other sedation regimens are possible [15,16]. Continuous monitoring of oxygen saturation along with EKG and frequent vital signs are essential any time a lung transplant patient is being sedated. Finally, inhaled metered-dose bronchodilators are frequently administered, and some institutions give preoperative steroids [15] or histamine antagonists [17].

Types of lung transplantation

Currently there are three surgical approaches commonly used in LT surgery, single-LT, bilateral- and bilateral-sequential LT, and heart-LT. Recently, successful living-donor lobar transplantation has also been described [18–20]. For nonseptic end-stage pulmonary disease, a single-lung transplant is most commonly chosen. This technique is technically easier and allows for the provision of donor lungs to two recipients. Single-LT has even been used successfully in recipients with pulmonary hypertension [21]. Double-LT can be performed using either an en bloc technique or a sequential technique involving two sequential single-lung transplants in the same operation. Double-LT is indicated primarily for cystic fibrosis and bronchiectasis, conditions that necessitate the removal of both infected lungs. Some centers also favor double-LT for recipients with pulmonary hypertension to avoid hyperperfusion and pulmonary edema in the transplanted lung, which is sometimes seen in these patients when a single lung is transplanted. Some practitioners recommend the

routine use of double-LT in young patients with end-stage emphysema because of improved survival and functional status in these patients after transplantation [22,23]. Heart-LT is performed with decreasing frequency as more diseases are treated successfully with isolated LT. This procedure is now reserved for patients with end-stage pulmonary disease and concomitant cardiac failure. Approximately 30 of these procedures are performed in the United States each year [1].

Immunosuppression and prophylactic antibiotics

Several immunosuppressive agents are usually given just before or during surgery. Three of the most common of these agents are steroids, cyclosporin A (CyA), and azathioprine [2]. Steroids broadly suppress T- and B-cell clonal expansion, cytokine production, and neutrophil activation. Generally, the calcineurin inhibitor CyA interferes with discrete T- and B-cell functions, and azathioprine inhibits nucleotide synthesis. The CyA dose is based on serum levels. Nephrotoxicity, hypertension, and neurotoxicity are common complications. The azathioprine dose is administered in fixed amounts and limited by side effects such as leukopenia, thrombocytopenia, and pancreatitis. In the case of rejection, mycophenolate mofetil, a selective inhibitor of both B cells and cytotoxic T cells, is generally used instead of azathioprine, and tacrolimus is substituted for CyA because it causes fewer side effects. Sirolimus is a newer agent that interferes with interleukin-2 signal transduction and appears to be significantly more potent than tacrolimus. Advances in interleukin-2 receptor inhibitors, newer monoclonal antibodies to inflammatory cells, and methods to produce chimerism between host and transplant to achieve immune tolerance are emerging tools in immunosuppression [24]. At the authors' institution, CyA is given in a loading dose (5 mg/kg by mouth if the creatinine level is $\leq$ 2 mg/dL or 2.5 mg/kg by mouth if the creatinine level is $\geq$ 2 mg/dL) on call to the operating room. Methylprednisolone is administered just before lung reperfusion (500 mg–1 g IV) and then prednisone or its equivalent is started at 100 mg twice daily and tapered. Azathioprine and CyA are also administered postoperatively in the ICU and thereafter. Variations of this regimen are typical at other centers [15,24]. A variety of prophylactic antibiotics are given before and after the procedure. These generally include agents directed at bacteria and viral and fungal agents; regimens tend to vary by institution.

Induction of anesthesia

There are several general principles involved in planning anesthesia for LT. Because of the emergent nature of the procedure, recipients may need "full stomach" precautions. These patients are at risk for postinduction hypotension resulting from decreased cardiac output from hypovolemia, vasodilation, and negative inotropic effects from the induction agents, worsening pulmonary

hypertension with right ventricular dysfunction or failure, and the negative effects of positive pressure ventilation on venous return. Furthermore, an epidural dose-test-dose given relatively close to induction of anesthesia may increase the possibility of hypotension.

Rapid-sequence or modified rapid-sequence inductions are generally performed in these patients. Thiopental has been used as an induction agent, especially in younger patients with normal heart function. However, thiopental has been avoided by the authors at their institution because it frequently results in hypotension, and has been associated with bronchospasm and pulmonary hypertension in some patients [25]. At the authors' institution, etomidate and succinylcholine are frequently used for rapid-sequence induction. Ketamine also is commonly used to avoid hypotension and may have other benefits including pulmonary vasodilation [26] and possibly anti-inflammatory properties [27,28], although it also may increase pulmonary vascular resistance [29]. For patients in whom a modified rapid-sequence induction is appropriate, slow titration of opiates during induction is used to reduce the effects of rapid withdrawal of sympathetic tone, which may result in cardiovascular collapse [30]. Muscle relaxants such as vecuronium are often used, especially if early extubation is planned. To maintain a mild tachycardia, pancuronium is preferred. This is often helpful to preserve cardiac output, especially in patients with right-heart failure, by avoiding distention of the right ventricle. A variety of vasopressors should be readily available even for patients with normal heart function [31]. Inotropic agents (milrinone, dobutamine), vasopressors (norepinephrine, phenylephrine, vasopressin), and vasodilators (nitroglycerin) or direct pulmonary vasodilators (prostacyclin, IV drip or aerosolized) [29,32] should be set up or readily available for patients with severe pulmonary hypertension or any degree of heart failure.

After induction of anesthesia, single-lung ventilation will be required. A left-sided double-lumen endotracheal tube (DLT) is commonly used for this purpose. The reliability of the DLT in achieving lung isolation generally makes it the preferred choice. The authors confirm correct DLT position by both auscultation and fiberoptic bronchoscopy. A single-lumen tube can be used in heart-lung transplants. When possible, a DLT is changed to a single-lumen tube at the end of the case.

The transition from spontaneous to positive pressure ventilation is the source of several serious problems that occur in patients with severe lung disease. Two primary goals are to avoid or minimize increases in pulmonary vascular resistance and the effects of positive pressure ventilation on air trapping or barotrauma. Meticulous efforts to prevent even short periods of hypoxia or mild hypoventilation, which can occur when initiating mechanical ventilation, will help to limit hypercapnia and the associated increase in pulmonary vascular resistance. To do this, patients are mildly hyperventilated to maintain an end-tidal carbon dioxide level of 30 mm Hg or a partial pressure (P_{CO_2}) of 28–30 mm Hg and an arterial pH range of 7.45–7.50. Using increased respiratory rates to induce mild hypocapnia may worsen the degree of air trapping. Smaller tidal volumes or a decrease in the respiratory rate may be necessary especially if hypotension is

produced. In unstable patients, pressure-limited modes of ventilation may reduce their risk of barotrauma, which at times may require an ICU ventilator. The risk of tension pneumothorax should be kept in mind, especially in patients with poor compliance and persistent hypotension. Nitrous oxide is generally avoided during single-lung ventilation and is contraindicated in patients with bullous emphysema in which nitrous oxide may expand air-containing spaces and increase pulmonary vascular resistance [29].

Maintenance of anesthesia

During the procedure, anesthesia is generally maintained with a balanced technique. Opiates that do not release histamine (fentanyl, sufentanil) and potent inhaled anesthetics with mild pulmonary vasculature relaxant effects (sevoflurane, isoflurane) [14,29] are often used with neuraxial blockade through the thoracic epidural catheter. In single-LT and double-LT in which CPB is unlikely and the patient is hemodynamically stable, many anesthesiologists will begin by using the thoracic epidural catheter. At their center, the authors frequently use mixtures of bupivicane (0.0625%–0.125%) with fentanyl, 10 μg/mL, or hydromorphone at an infusion rate of 3 to 6 mL/h. In this manner reduction of the use of systemic opiates and higher concentrations of inhalational anesthesia is attempted.

Avoiding excessive fluid administration is extremely important. Because noncardiogenic pulmonary edema in the reimplanted lungs is frequent, patients are generally maintained in a normovolemic or slightly hypovolemic state. Both pulmonary artery occlusion pressures (generally in the range of 10–15 mm Hg) and transesophageal echocardiographic evaluations of left ventricular filling are used at the authors' institution to avoid overdistention of the ventricle.

To reduce bleeding, ε-aminocaproic acid (Amicar), 10 g IV, is often administered after induction, and another 10 g IV is administered after reimplantation. Significant bleeding can be anticipated with bilateral LT, especially for cystic fibrosis patients in whom significant adhesions are present, patients with repeat thoracotomies, or when cardiopulmonary bypass is required. In these settings, an aprotinin infusion (2 million kallikrein inhibitor units [KIU] over 20 minutes and 0.5 million KIU every hour until surgery is finished) is frequently used to decrease bleeding [15,33,34] and possibly to reduce the effects of the inflammatory cascade [35]. Many centers also set up a rapid infuser system to provide rapid resuscitation with blood products. When blood transfusions are necessary, there are data suggesting that transfusions before reperfusion of the new lung may reduce the risk of transfusion-related lung injury and the effects of hypervolemia on the new lung [36].

To anticipate the effects of pulmonary artery clamping, surgeons frequently manually occlude the pulmonary artery and evaluate the effects on the pulmonary artery pressure (PAP) and right ventricular function. The anesthesiologist should monitor changes in the PAP, rises in central venous pressure (CVP), or decreased

cardiac output. Transesophageal echocardiography can be used to directly evaluate right ventricular function, distention, new tricuspid regurgitation, and when possible, to estimate right ventricular cardiac output. If severe hemodynamic derangements are observed, cardiopulmonary bypass is often required and may be related to improved outcomes [37].

Increasingly, the authors are attempting to extubate patients early [9]. Using shorter acting agents (eg, propofol, remifentanil, sevoflurane) and, if appropriate, a thoracic epidural have allowed us, in some circumstances, to extubate patients in the operating room or shortly after arrival in the ICU. Strict criteria must be met to accomplish early extubation, including good pulmonary function from the new lung (PaCO2 ÷ fraction of inspired oxygen [$Fi0_2$] $\geq$ 300 mm Hg, $P_{CO_2} \leq$ 60 mm Hg), no signs of reperfusion injury, hemodynamic stability, temperature greater than 36°C, and no other significant hemodynamic support during the procedure [9]. Noninvasive modes of ventilatory support are sometimes used for these patients after early extubation [9,32]. More typically, at the end of surgery, the DLT is removed and a single-lumen tube is placed. Following this exchange of tubes, flexible bronchoscopy is performed to evaluate the bronchial anastomoses and clear the airways of blood, secretions, and mucus.

Specific intraoperative problems

In patients with a ''difficult airway,'' several options exist to successfully manage the airway. Patients can be intubated with fiber-optic assistance followed by DLT placement over a tube exchanger. At their institution, the authors have had most success with the snare-guided endobronchial blocker (Arndt endobronchial blocker, Cook Critical Care, Bloomington, Indiana) that requires a flexible bronchoscope to pass through the bronchial blocker (BB) loop. After directing the bronchoscope to the correct bronchus, the BB is guided by the snared loop into the proper location, and the position is confirmed as the bronchoscope is withdrawn. Another variation on a BB is the Univent (Fuji Systems, Tokyo, Japan) bronchial blocker tube, which can be relatively easily manipulated to block the left main bronchus but requires more practice on the right side because of the right upper lobe bronchus. The advantage of either type of bronchial blocker, compared with a DLT, is that only one endotracheal tube is needed for the procedure, and an endotracheal tube conversion is avoided at the end of the procedure. Other options include using a stand-alone BB passed through or around a single-lumen endotracheal tube. To achieve optimal lung deflation, both lungs should first be allowed to deflate by briefly disconnecting the endotracheal tube and then inflating the BB balloon. Even in the ideal setting, bronchial blockers can be difficult to direct and position, can be easily dislodged, and often do not adequately allow for lung deflation because of the small internal channel.

The most common problems associated with both single- and double-LT generally involve ventilation-perfusion mismatch and pulmonary artery hypertension with or without right ventricular failure. Strategies to avoid or overcome

the hypoxemia commonly seen during single-lung ventilation in thoracic anesthesia are important. Obviously, 100% oxygen is used despite concerns that it may add to reperfusion injury [36]. Hypoxic pulmonary vasoconstriction may be improved by reducing concentrations of inhalational anesthetics [29] and avoiding vasodilators such as nitroglycerin. Continuous positive airway pressure to the surgical lung frequently corrects hypoxemia, although occasionally positive end-expiratory pressure (PEEP) in the ventilated lung may also be required [38]. In the setting of intractable hypoxemia, cardiopulmonary bypass is occasionally required until the donor lung has been implanted and is functioning properly.

In patients with pre-existing or recent onset pulmonary hypertension, the institution of single-lung ventilation signals the start of the most challenging period for the anesthesiologist. At the time of pulmonary artery clamping, increased PAP are often encountered. It is important to monitor PAP, CVP, and, when possible, right ventricular function with transesophageal echocardiography. Cardiac output and other parameters of end-organ perfusion such as urine output may be helpful. Methods to reduce PAP include fluid restriction, intravenous arterial dilators such as nitroglycerin or sodium nitroprusside, and direct pulmonary artery relaxants such as prostaglandin E_1, prostacyclin, and inhaled nitric oxide (iNO). Inhaled or infused sildenafil (Viagra) has been demonstrated to have an additive effect to iNO and may be used more often in the future [39,40]. At their institution, if PAP increases significantly with pulmonary artery clamping or with single-lung ventilation, the authors first start intravenous nitroglycerin, but then rapidly institute iNO at 80 ppm and titrate to 20 ppm if the PAP does not improve or systemic hypotension ensues. iNO has not been shown to reduce reperfusion injury after transplantation or to reduce the mortality associated with adult respiratory distress syndrome, but it has been shown to improve pulmonary artery pressures and oxygenation in patients who develop reperfusion injury [34,36]. In the situation in which pulmonary hypertension is not treatable or right heart failure is worsening with low cardiac output, cardiopulmonary bypass is generally required.

At the time of reperfusion, methylprednisolone (Solu-Medrol), 1 g IV, is given. Other institutions may also use mannitol not only for its diuretic properties, but also for its free-radical superoxide-scavenging activity [17]. When the implanted lung is re-expanded, a slow continuous airway pressure breath is used to reduce the effect of rapid re-expansion and barotrauma. Once on the ventilator, the patient's airway pressures are monitored to keep peak pressures less than 40 mm Hg and plateau pressures less than 35 mm Hg. It is not uncommon for acute hyperemia to follow reperfusion with washout of free radicals and other inflammatory cytokines. Some centers purposely maintain systemic arterial blood pressures on the slightly lower side (systolic pressure range of 80–90 mm Hg) to avoid bleeding and reduce PAP. Fortunately, PAP frequently decreases significantly after reperfusion of the lung. In the case of acute lung injury or transfusion-related lung injury, patients frequently manifest significant amounts of pulmonary edema with persistent hypoxemia, elevated pulmonary artery pressures, and potentially decreased cardiac output. Although

this event is often extremely difficult to manage, it will usually improve over several hours. Vasopressor and inotropic support and iNO usually are needed. The authors also undertake aggressive diuresis in these patients and occasionally transfuse packed red blood cells to maintain a hematocrit of 30%–35%, especially if mixed venous oxygen saturation is below 65%. In the most extreme examples, ECMO or high-frequency jet ventilation may be the only mechanism to oxygenate and clear carbon dioxide. Alternatively, when other modalities are not available, individually ventilating each lung with a DLT and two ventilators is possible.

Postoperative care

Respiratory management and mechanical ventilation

Most lung transplant recipients remain intubated and mechanically ventilated for 24–72 hours in the immediate postoperative period. By 24 hours many patients can be extubated; however, patients with some impairment of graft function, poorly trained respiratory muscles, phrenic nerve injury, inadequately treated pain, or unstable hemodynamics may still require assisted ventilation beyond this time. The aim of mechanical ventilation is to maintain adequate oxygenation using low airway pressures to avoid barotrauma, volutrauma, and anastomotic dehiscence. Whether to use a pressure-limited or a volume-controlled ventilator mode is a less important consideration than keeping tidal volumes in the range of 6–8 mL/kg and plateau airway pressures at less than 35 mm Hg. PEEP is generally kept to minimal levels ($\leq$ 5 mm Hg) unless significant ventilation-perfusion mismatching is present, which can occur in patients with poor graft function caused by reperfusion injury. In this situation, PEEP levels of 10–18 mm Hg may improve oxygenation and allow reduced $Fi0_2$ levels.

Special pulmonary management strategies may be required for certain populations of patients who receive a single-lung transplant. There is an increased risk of noncardiogenic reperfusion pulmonary edema among patients with primary pulmonary hypertension. The mechanism for this event is preferential ''luxury'' perfusion of the transplanted lung with low pulmonary vascular resistance compared with the native diseased lung. This condition results in unilateral pulmonary edema and respiratory failure. Reperfusion injury is more common in the reimplanted lung but sometimes occurs in the native lung as well. Also called reimplantation injury or primary graft failure, this condition is usually mild; however, in 15% of patients it can be severe [41,42]. It is characterized by alveolar infiltrates observed in newly obtained radiographs, a reduction in pulmonary compliance, and compromised gas exchange in the absence of other factors such as infection, elevated wedge pressure, and rejection. Radiographic findings typically include patchy alveolar consolidation or dense perihilar and basilar alveolar consolidation with air bronchograms. The mechanism for reperfusion injury is poorly understood but is postulated to be

caused by lung injury occurring during the preservation period or following reperfusion with disruption of lymphatics, bronchial vasculature, or nerves. Animal studies have suggested that the severity of this disorder may be related to the duration of ischemia and the resulting production of toxic oxygen free radicals. Reperfusion injury may be minimized by optimizing organ preservation and avoiding prolonged ischemia. The differential diagnoses include acute rejection, cardiogenic pulmonary edema, or infection, but the time course of development, immediate to 6 hours after transplantation, usually suggests reperfusion injury.

Management of reperfusion injury includes careful hemodynamic monitoring, diuresis, and inotropic agents. For severe cases, iNO, differential lung ventilation, or ECMO may be required [43,44]. The mechanism of the beneficial effects of iNO in the setting of reperfusion injury is caused by the delivery of nitric oxide to ventilated lung segments only, allowing selective vasodilatation in these areas with improved ventilation-perfusion matching [45,46].

Another potential problem arising after transplantation of a single lung is overinflation of the native lung, especially if the transplanted lung has severely decreased compliance from reperfusion or the native lung is especially compliant, such as in patients with bullous emphysema, which may result in significant ventilation-perfusion imbalances. Overinflation has been successfully managed using selective ventilation of the different lungs [47] and with ECMO [48]. Hyperinflation of the native lung may also occur as a late consequence (within months) of single-LT, and this has been treated successfully with volume reduction surgery on the native lung [9,49]. Early extubation is also the preferred treatment if gas exchange is reasonable. After every lung transplant, patients undergo thoracic radiography. The parenchymal structure, the presence of edema or atelectasis, pneumothorax, lung expansion and size, and position of the diaphragm and mediastinum can be assessed (Table 1) [50].

Airway complications occur following LT [51]. Anastomotic dehiscence, stenosis, and bronchomalacia are the major concerns [52]. Partial or complete dehiscence may be detected by the presence of mediastinal emphysema on chest radiograph or on CT scan. Anastomotic technique and lung preservation have proven to be causative factors in airway complications, but the recipient's age, gender, and disease have not proven to be risk factors. Therapeutic

Table 1
Interpretation of chest radiographs after lung transplantation

Radiographic appearance of infiltrate	Time of onset (<24 h)	Time of onset (>24 h)
Diffuse	Over-hydration; reperfusion injury	Over-hydration; rejection; late reperfusion injury
Localized	Surgical residua; localized graft injury; hemorrhage; pleural fluid accumulation	Pneumonia; pleural fluid accumulation
Lobar	Vascular problem; obstructing clot	Vascular problem; sputum plug; pneumonia

options include balloon dilatation, stent placement, laser treatment, and occasionally surgery.

Hemodynamic management

During LT, many patients require inotropic (milrinone) or vasopressor support (norepinephrine, vasopressin) to maintain hemodynamic stability while avoiding large fluid volumes to keep the lungs "dry." The many potential causes of low blood pressure and cardiac output, however, should be addressed as well (Box 3). Blood transfusion is kept to a minimum to reduce the risk of transfusion-related acute lung injury. If the operation was performed on CPB, correction of all intraoperative disturbances of fluid balance is a priority within these first postoperative hours. Hemodynamic surveillance using Swan-Ganz catheter monitoring assists in the detection and treatment of untoward events such as alarming changes in the PAP or decreases in cardiac output. The usual strategy is

Box 3. Important causes of inadequate cardiac output after lung transplantation

Immediate postoperative

Hypovolemia
Hemorrhage
Hypothermia
Analgesia or sedation (particularly epidural-related)
Pneumothorax
Dynamic hyperinflation of remaining native lung
Oversized pulmonary allograft
Coronary artery air embolism
Pulmonary venous or arterial anastomotic obstruction (ie, embolism, clot, stitch, torsion)
Pulmonary embolism (ie, thrombus, air)

Delayed (after 24–48 h)

Myocardial infarction
Arrhythmia
Left ventricular dysfunction (ie, nonspecific)
Sepsis (particularly line- or occult gut-related)
Anaphylaxis
Transfusion reaction
Hyperacute rejection

to keep pulmonary artery occlusion pressures low, which is important to avoid alveolar flooding. Monitoring of cardiac function can be augmented by transesophageal echocardiography especially in patients transplanted for primary pulmonary hypertension with poor native ventricular function. Elevated PAP is frequently seen after LT resulting from a variety of reasons, especially with early primary graft dysfunction. In this situation, the use of iNO lowers pulmonary artery pressures and diminishes intrapulmonary shunting [53,54]. Patient positioning has a clear influence on the functional behavior of the transplanted lung. Elevation of the upper body helps to reduce cardiac preload, improve lung inflation, and lower pulmonary artery pressure.

Sedation and Pain relief

In the immediate postoperative period, most lung transplant patients are on infusion regimens of short acting sedatives such as propofol from which they can be rapidly weaned to facilitate discontinuation from mechanical ventilation. Adequate pain relief using epidural infusions of local anesthetics and narcotics greatly facilitates early extubation. Epidural analgesia avoids the complications associated with systemic analgesics. In addition, proper analgesia improves early pulmonary function [55]. The pulmonary allograft recipient needs to be able to move freely and cough to clear secretions, particularly given the absence of normal cilial airway clearance mechanisms in the allograft and the significant restriction imposed by drainage tubes. Uncontrolled pain will predispose to atelectasis, sputum retention, and, ultimately, infection. Peripheral infusions of intravenously administered opiates may be used for patients without an epidural catheter. Other analgesics, including nonsteroidal anti-inflammatory agents and cyclooxygenase-2 inhibitors, are opiate-sparing and can be helpful except in patients with renal failure.

Renal management

An intraoperative fluid management strategy using limited hypovolemia, judicious inotropic support, or vasopressors and diuretics runs the risk of renal hypoperfusion. In the first few days after surgery, it is common to note oliguria and elevated serum levels of urea and creatinine. There are many potential explanations for posttransplant renal dysfunction (Box 4). The most common clinical scenario occurs at day 3 when the requirements for dry lungs, immunosuppressive medications and possible aminoglycoside use must be balanced against developing renal insufficiency. Optimization of renal function includes careful fluid management that may require pulmonary artery monitoring, level-targeted and focused antibiotic therapy, and alternative immunosuppressive strategies. Recent studies suggest that 10% of all lung transplant survivors will develop end-stage renal disease at 5 years and that creatinine clearance at 1 month predicts renal function at 5 years [37,56]. Patients with cystic fibrosis may have

Box 4. Causes of renal dysfunction after lung transplantation

Preoperative causes

- Underlying chronic renal impairment related to hypertension diabetes and drugs (ie, aminoglycosides, diuretics, aspirin, and nonsteroidal anti-inflammatory agents)
- Renal hypoperfusion related to inadequate cardiac output (pulmonary hypertension)

Perioperative and postoperative causes

- Hypovolemia or hypotension
- Vasopressor agents
- Drugs (ie, aminoglycosides, immunosuppressive [calcineurin inhibitors], and non steroidal anti-inflammatory agents)
- Transfusion reactions

higher risks of developing renal failure, despite being younger than most other lung transplant recipients, probably because of a high incidence of diabetes and aminoglycoside toxicity.

Gastrointestinal management

Gut function may be significantly impaired both acutely and chronically after LT. It has been demonstrated that 40% of LT recipients have gastrointestinal symptoms after transplantation [57]. In the first few days the acute effects of anesthesia, narcotics, inotropic agents and electrolyte shifts can lead to a small bowel ileus, which can present as large bowel constipation and cecal perforation related to relative immobility, fluid shifts, and the use of analgesics, inotropic agents, and high-dose corticosteroids [58]. Importantly, in the LT setting, such an occurrence may initially be clinically relatively subtle, so additional supporting radiographic features need to be specifically sought. The incidence of gastroesophageal reflux is also high in the lung transplant group, and there is increasing evidence linking this condition to chronic allograft damage by possible aspiration. These problems can be at least partially relieved by promotility agents and by elevating the head of the patient's bed by more than 30°. Distal intestinal obstructive syndrome is of a particular concern in patients with cystic fibrosis [59]. Oral *N*-acetylcysteine, an osmotically active bowel preparation or meglumine diatrizoate (Gastrografin) enemas may even be required. Cystic fibrosis patients will need to take oral pancreatic supplements and immunosuppressants postoperatively. Hyperglycemia and new onset diabetes may be related

to postoperative corticosteroid therapy. Presumably related to fluid shifts, postoperative liver function tests can show a cholestatic picture, which improves spontaneously, but oral ursodeoxycholic acid may be helpful.

Complications

Immunologic complications

Acute rejection can develop in up to 50% of patients in the first postoperative month and in as many as 90% of patients in the first postoperative year [60]. The risk of acute rejection is greatest in the first 100 days after transplantation. Clinically, rejection presents with cough, shortness of breath, fever, and impaired oxygenation. Occasionally, the patient can be asymptomatic, and rejection is suggested only by a reduction in pulmonary function. Physical examination may be unremarkable or may reveal rales or wheezing. Radiographically, pleural effusions and interstitial opacities may be detected during the first month following transplantation. Bronchoscopy with transbronchial biopsy is performed when acute rejection is suspected. The characteristic pathology accompanying acute lung transplant rejection is a lymphocytic vasculitis. Occasionally, acute rejection can progress to respiratory failure that requires mechanical ventilation, but generally, acute rejection is easily treated with augmentation of immunosuppression [24,61].

In LT, the pathologic hallmark of chronic rejection is the bronchiolitis obliterans syndrome (BOS), which is suggested by a fall in FEV_1 to less than 80% of the peak value [62]. BOS is a leading cause of morbidity and mortality beyond the first year after transplantation. The incidence of bronchiolitis ranges from 35% to 50%, and nearly 70% of patients surviving 5 years after transplantation will develop BOS. The risk of mortality within 2 years following the diagnosis at any stage is 40% [63]. The histologic trademark of chronic rejection is fibrous obliteration of endothelial structures. Chronic rejection is the result of prolonged and multiple acute rejection episodes and possibly cytomegalovirus (CMV) infection. The presentation of BOS is nonspecific and may consist of symptoms like those seen with upper respiratory tract infection. Pulmonary function tests show worsening obstructive dysfunction. The chest radiograph is typically unchanged from baseline or may show some hyperinflation. A high-resolution CT scan may confirm hyperinflation, air trapping, and bronchiectasis. Diagnosis can be made with transbronchial biopsy. Other possible causes for worsening pulmonary function must be excluded.

The onset of BOS is usually insidious and progresses slowly, so respiratory failure develops late. Treatment for this condition has focused on prevention rather than a post-diagnosis treatment. The key to the prevention of acute rejection is early aggressive immunosuppression [63], but this predisposes to recurrent and opportunistic infections, which can then lead to respiratory failure.

Infectious complications

The incidence of infection in lung transplant recipients is higher than that reported in other solid organ transplants [24,64]. Infections (bacterial and viral) account for 45% to 50% of all deaths [65], resulting mainly from a diminished cough reflex secondary to denervation, poor lymphatic drainage, decreased mucociliary clearance, or infection harbored by the recipient in the setting of immunosuppressive therapy [15]. Bacterial pneumonia is the most common infection in lung transplant patients. The prevalence has been nearly 35% during the first few postoperative weeks; routine prophylaxis can reduce that amount to 10% [66].

An infectious tracheobronchitis may develop at the anastomosis site because there is no direct revascularization of the bronchial vessels, and thus the anastomosis is subject to ischemia [5]. Infections that develop at the anastomosis are most commonly caused by bacterial organisms such as *Staphylococcus* or *Pseudomonas*, or fungal organisms, primarily *Candida* and *Aspergillus*. Eventual anastomotic stenosis or bronchomalacia can develop after resolution of the infection.

Cytomegalovirus (CMV) is the most common viral infection in the lung transplant recipient [5]. Because more than half of all adults in the United States are seropositive for CMV, the risk of donor-to-recipient transmission can occur by transplantation, blood transfusion, or reactivation of a latent virus in a seropositive recipient. The incidence of illness, which includes both infection and disease, may be as high as 50%. Those patients who are CMV-negative and receive a lung from a CMV-positive donor are at the highest risk of CMV infection, with an incidence as high as 85%. The spectrum of presentations of CMV infection is variable, from asymptomatic shedding to an acute pneumonic process requiring mechanical ventilation for respiratory failure. Treatment includes ganciclovir and CMV hyperimmunoglobulin.

Fungal infections also are more common in the lung transplant recipient than in other solid organ transplant recipients, and the incidence may be as high as 10% to 22% [66]. Two species of fungi, *Candida* and *Aspergillus*, have been found to colonize pulmonary transplant specimens. Many LT programs now routinely institute prophylaxis with azole agents, usually itraconazole. *Candida* is the most common lung transplant fungal infection. *Aspergillus* may invade blood vessels and present with pulmonary infarcts or hemoptysis. *Aspergillus* disease has high mortality. Treatment includes amphotericin or a liposomal amphotericin agent.

Posttransplant lymphoproliferative disorders

Posttransplant lymphoproliferative disorder (PTLDs) is a heterogeneous group of tumors that are more common after LT than other solid organ transplants [65]. Tumor types include lymphomas, skin carcinoma, perineal carcinoma, cervical cancer, and Kaposi's sarcoma. The most frequent form of PTLD is a B cell non-

Hodgkin's lymphoma. Its development is strongly associated with Epstein-Barr virus (EBV). EBV-negative recipients of an EBV-positive organ are most likely to develop this infectious complication. Children tend to be at higher risk because they are often EBV-negative. PTLD occurs in approximately 6% of lung transplant recipients, with most cases developing in the first postoperative year [67]. The lung allograft is the most common site of involvement, and it is usually multifocal in nature. The characteristic radiographic findings are solitary or multiple pulmonary nodules, and disseminated disease affecting the central nervous system, skin, and other extrapulmonary sites has been reported. Treatment for PTLD includes a reduction in immunosuppression, antiviral therapy, radiation or chemotherapy as appropriate for lymphoma, and adoptive immunotherapies extrapolated from the bone marrow transplant population. PTLD or its treatment can lead to respiratory failure in the lung transplant population [68].

New directions and controversies

The donor supply mismatch has a more profound effect on those who require bilateral LT for suppurative lung disease, such as cystic fibrosis, in which up to 50% of patients die while on the waiting list. Living lobar-LT is used in some centers as an alternative to cadaveric LT, primarily for cystic fibrosis [69]. In living lobar LT, two healthy donors are selected, one to undergo removal of the right lower lobe and the other removal of the left lower lobe. These lobes are then implanted in the recipient in place of the whole right and left lungs. This technique has been demonstrated to benefit a small group of patients who would have succumbed to disease while waiting for a cadaveric donor. The main challenges include the size disparity between the donor lobe and recipient pleural thoracic cavity and the overabundant blood flow (the entire cardiac output) supplying the two relatively undersized lobes. The overall survival at 1, 3, and 5 years is 67%, 51%, and 48%, respectively for adult recipients.

The donor supply mismatch could also be reduced if pulmonary xenotransplantation becomes feasible. Currently, however, pulmonary xenografts are rapidly rejected by mechanisms that are dependent on the expression of antigens by the donor, which are recognized by complement-activating xenoreactive antibodies in the recipient and by mechanisms distinct from those causing hyperacute rejection of other organs, including the greater susceptibility of the lung to complement anaphylatoxins, the presence of pulmonary intravascular macrophages, and activation and dysregulation of the coagulation system [43]. By understanding these barriers, prolonged xenograft survival has been achieved in experimental studies. Human trials remain in the distant future.

Improving the treatment for pulmonary artery hypertension (PAH) may reduce the need for LT among these patients [70]. Over the last years, several multicenter, randomized controlled trials have shown that prostaglandin I_2 derivatives (treprostinil, iloprost, and epoprostenol) and the dual endothelin-receptor antagonist bosentan improve exercise tolerance and symptoms of severe

PAH [37,53–56]. These medical therapies have encouraging short- and mid-term clinical benefits. The therapeutic choice should be based on indicators of prognosis, appropriate risk-benefit ratio, and patient preference. Long-term efficacy and a survival benefit, however, have not yet been uniformly reported. Medical treatment is, therefore, recommended as the first step for treating PAH and may replace or postpone LT. LT, however, will still remain the ultimate option for a significant number of patients with end-stage PAH.

A final new direction is the development of improved immunosuppression, ideally by inducing tolerance in the recipient to the transplanted organ. LT is limited by the inadequacy of current immunosuppression, which allows ongoing injury to the transplanted organ through immunologic attack, and the toxicity of immunosuppression, which causes organ dysfunction, malignancy, and infection. Tolerance to donor-specific antigens holds the promise for prolonging graft function and limiting these toxicities. Using methods that have been successful at achieving tolerance in the laboratory (including administration of depleting or blocking agents and those that involve the injection of immunomodulatory cellular populations), tolerance strategies are being applied in humans with success [57].

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