



A Review of Anesthesia for Lung Transplantation

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Lung transplantation is the only treatment option for patients with end-stage lung disease. Although more than 4,000 lung transplants are performed every year worldwide, the standardized protocols contain no guidelines for monitoring during lung transplantation. Specific anesthetic concerns are associated with lung transplantation, especially during critical periods, including anesthesia induction, the initiation of positive pressure ventilation, the establishment and maintenance of one-lung ventilation, pulmonary artery clamping, pulmonary artery unclamping, and reperfusion of the transplanted lung. Anesthetic management according to the special risks associated with a patient's existing lung disease and surgical stage is the most important factor. Successful anesthesia in lung transplantation can improve hemodynamic stability, oxygenation, ventilation, and outcomes. Therefore, anesthesiologists must have expertise in transesophageal echocardiography, extracorporeal life support, and cardiopulmonary anesthesia and understand the pathophysiology of end-stage lung disease and the drugs administered. In addition, communication among anesthesiologists, surgeons, and perfusionists during surgery is important to achieve optimal patient results.

Keywords: Anesthesia, Lung transplantation

Introduction

Lung transplantation is the only known treatment option for patients with chronic severe lung diseases when existing non-surgical treatments are ineffective [1,2]. Idiopathic interstitial pneumonia, chronic obstructive pulmonary disease, and cystic fibrosis are the most common diseases in patients who receive lung transplantation. Although the first human lung transplant was reported by Hardy et al. [3] in 1963, the first successful lung transplantation was not reported until 1983, and it has been supported by immunosuppressants, organ preservation, and anesthesia methods [4]. Since the mid-1990s, lung transplantation has made rapid progress in quantity and quality with the development of immunosuppressive drugs; 47,647 adult lung transplants and 3,772 adult cardiopulmonary transplants had been performed as of the end of June 2013. More than 4,000 lung transplants are performed every year worldwide [5].

Novel immunosuppressive agents to prevent post-trans-

plant rejection, the use of new drugs and selective pulmonary arterial dilators, and advances in patient monitoring devices for intraoperative anesthesia management have made an impact. Lung transplantation due to purulent, obstructive, restrictive, and vascular lung disease requires special management methods, including patient evaluation, premedication, intraoperative monitoring, vascular access, anesthesia induction, management of reperfusion, and postoperative pain management. In particular, anesthetic management according to the special risks associated with a patient's existing lung disease and the surgical stage is the most important factor. The median survival rate after lung transplantation is 6.7 years [6], and approximately 20% of patients die in the first year after transplantation due to infection, primary graft dysfunction (PGD), and multiple organ failure [7].

Successful anesthesia during lung transplantation can improve hemodynamic stability, oxygenation, ventilation, and outcomes. Therefore, in this review, we summarize the considerations for anesthesia in lung transplantation.



Preparation before surgery

Indications for lung transplantation

Due to the scarcity of donor organs, patient selection for lung transplantation is important. To help clinicians determine appropriate candidates, the International Society of Heart and Lung Transplantation has published a consensus document on lung transplant candidate selection [8]. Lung transplantation can be considered for patients with chronic end-stage lung disease who have a >50% risk of death from lung disease within 2 years, but have a high probability (>80%) of surviving for 5 years after transplantation, from a general medical perspective [9]. The contraindications for lung transplantation are described in Table 1 [8,9].

Patient evaluation

When a patient is considered a viable candidate, a physical, social, and psychological assessment must be conducted by a multidisciplinary team of pulmonologists, thoracic surgeons, infectious disease specialists, nurses, nutritionists, physiotherapists, psychologists, and social workers.

Pulmonary rehabilitation should precede surgery, and appropriate nutritional support is required for patients with a low body mass index. End-stage lung disease is extensive; includes suppurative, obstructive, restrictive, and pulmonary blood vessels; and requires disease-specific anesthesia management. Patients' current status can be checked by a pulmonary function test, transthoracic echocardiography, perfusion lung scan, and cardiac catheterization (Table 2) [10].

A ventilation-perfusion scan provides information about which lung can better tolerate one-lung ventilation, thus helping to decide which lung to transplant first. End-stage pulmonary disease is often accompanied by cardiovascular failure, with right ventricular (RV) dysfunction and the presence of pulmonary hypertension (mean pulmonary artery [PA] pressure ≥ 25 mm Hg), and patients may not tolerate hypoxemia, hypercapnia, and hemodynamic instability during surgical manipulation and PA clamping [11,12].

It is important to identify high-risk patients in order to establish an appropriate plan for the surgical technique. The characteristics of high-risk recipients are as follows: extracorporeal membrane oxygenation (ECMO) before surgery, oxygen requirement >5 L/min, retransplantation,

Table 1. Contraindications to lung transplantation [8,9]

	Contraindications
Absolute	Recent malignancy
	Significant dysfunction in another major organ system
	Acute unstable medical condition
	Uncontrolled bleeding
	Chronic uncontrolled multidrug resistant infection or active tuberculosis
	BMI >35 kg/m ²
	Significant chest wall or spinal deformity
	Alcohol or drug abuse
	Psychiatric or psychological conditions associated with a lack of ability to cooperate with care
	Non-adherence to medical therapy
	Lack of a support team
	Limited rehabilitation potential
	Relative
BMI 30–34.9 kg/m ²	
Severe malnutrition	
Mechanical ventilation or extracorporeal life support	
Infection with highly resistant organisms	
Hepatitis B or C without significant hepatic damage	
HIV infection with undetectable HIV-RNA	
Atherosclerotic disease with risk of end-stage heart disease	
Severe osteoporosis	
Inadequately controlled type 2 diabetes, hypertension, or gastroesophageal reflux disease	
Extensive previous chest surgery with lung resection	
Psychiatric or psychological condition that has the potential to affect medical care	

BMI, body mass index; HIV, human immunodeficiency virus.

Table 2. Standard evaluation for lung transplant candidates [10]

	Methods
Pulmonary evaluation	Pulmonary function testing
	Arterial blood gas on room air
	Chest radiography
	6-Minute walk distance test
	Non-contrast computed tomography scan
	Quantitative ventilation and perfusion scan
Cardiac evaluation	Fluoroscopy of the diaphragm
	Electrocardiogram
	Right heart catheterization
	Echocardiogram with bubble study
	Left heart catheterization for age >40 years or computed tomography coronary angiography for age >40 years
Gastrointestinal evaluation	Cardiac magnetic resonance imaging (for patients with lung sarcoidosis)
	Barium swallow
	24-Hour pH probe testing
	Esophageal manometry
	Solid gastric emptying (if there is a concern for gastroparesis)
Laboratory testing	Liver ultrasound (age 55 years)
	Routine hematologic, chemistry, and coagulation studies
	Viral serologies for the following: cytomegalovirus; herpes simplex virus; Epstein-Barr virus; varicella zoster virus; hepatitis B, C; human immunodeficiency virus
	Flow cytometry for human leukocyte antigen antibodies

age >70 years, renal impairment, hepatic impairment, severe pulmonary hypertension, high or low body mass index, and chronic use of corticosteroids [9,13,14]. In addition, donor-related characteristics associated with high risk are a female donor for a male recipient, a donor/recipient weight ratio <0.7, a donor-recipient cytomegalovirus mismatch (donor positive/recipient negative), and a history of smoking or diabetes [13,14].

Pretreatment

Immunosuppressive induction should be started before surgery [15], and routinely taken medications, including bronchodilators, antibiotics, and pulmonary vasodilators, need to be continuously administered. If the patient is receiving intravenous prostaglandin, it should be continued until extracorporeal life support (ECLS) is started. The administration of sedatives outside the operating room is not recommended because there is no reserve of lung function, and sedatives can cause acute right heart failure or cardiopulmonary arrest due to hypoxia, hypercapnia, and increased pulmonary vascular resistance (PVR) [15].

Thoracic epidural analgesia

Adequate analgesia after surgery is important to promote extubation, and thoracic epidural analgesia has a better an-

algesic effect than systemic opioid analgesics. However, when an epidural catheter is inserted before surgery, there is the risk of a hemorrhagic puncture, an increase in the size of the epidural hematoma due to the use of heparin, and a delay in clinical signs and appropriate decompression surgery. Therefore, the risks and advantages of thoracic epidural analgesia should be carefully discussed and selected [16].

Monitoring and vascular access

Although several lung transplant centers perform 4,000 lung transplants per year [6], the standardized protocols contain no monitoring guidelines [17]. Peripheral intravenous access, pulse oximetry, electrocardiography, and non-invasive blood pressure apparatuses are applied before anesthesia induction, and the following parameters are also monitored: right radial artery pressure, central venous pressure through the right internal jugular vein, PA pressure, transesophageal echocardiography for the evaluation of cardiac function during surgery, continuous cardiac output, mixed venous blood oxygen saturation, continuous arterial blood gas monitoring, and the bispectral index. Among these, the arterial pressure, central venous pressure, PA pressure, and transesophageal echocardiography (TEE) are considered essential to monitor during surgery [18,19]. TEE allows the evaluation of RV and left ventricu-

lar (LV) function and helps identify possible deviations from ECMO used for hemodynamic support during lung transplantation. If TEE confirms that there is no narrowing of the pulmonary vascular anastomosis after reperfusion, the cause of hypoxia may be a rejection or reperfusion injury [20]. Temperature monitoring is also important because hypothermia can exacerbate pulmonary hypertension and blood clotting disorders, as well as delaying extubation of the endotracheal tube (ETT) [21,22].

Anesthesia induction

Anesthesia induction must be preceded by denitrogenation or preoxygenation. In end-stage lung disease, due to the ventilation/perfusion imbalance, denitrogenation and end-tidal concentrations of inhaled anesthetics can be achieved slowly. Even if preoxygenation is performed, rapid hypoxia and hypercapnia, increased PVR, and RV failure may occur because the respiratory reserve is low [16]. Therefore, surgeons and perfusionists who can perform sternotomy for emergent ECMO or cardiopulmonary bypass (CPB) in case of severe cardio-respiratory instability must be available [23]. The hemodynamic goals of anesthesia induction are to maintain systemic vascular resistance and myocardial contractility and to prevent an increase in PVR [24]. This can be achieved through opioid-based balanced anesthesia. Considering a patient's condition during anesthesia induction, hypnotics (e.g., midazolam, etomidate, propofol, and ketamine) and opioid analgesics may be used.

A double-lumen endotracheal tube (DLT) or a single-lumen ETT with a bronchial blocker may be used, although a left-sided DLT is usually used because it offers good surgical flexibility, the opportunity for bronchial washing, and one-lung ventilation after reperfusion [25]. When changing to a single-lumen ETT at the end of surgery, the use of a tube exchange catheter is recommended in consideration of airway edema.

Mechanical ventilation

Since most patients with obstructive pulmonary disease have emphysema, there is a high likelihood that they have accompanying cardiovascular disease. In addition, caution should be exercised during positive pressure ventilation or central venous catheterization because there is a high risk of pneumothorax. It is necessary to prolong the expiratory time to prevent overinflation of the lungs and the consequent decrease in venous return and collapse of circulation

[15]. Due to alveolar dead space, the end-tidal carbon dioxide partial pressure may differ from the actual arterial carbon dioxide partial pressure. Therefore, frequent arterial blood tests and proper ventilation should be performed.

In order to reduce lung damage in patients with adult respiratory distress syndrome, a tidal volume of 6–8 mL/kg should be used, and hypercapnia can be allowed (permissive hypercapnia) [26]. In patients with restrictive lung diseases such as idiopathic pulmonary fibrosis, connective tissue disease, or drug- or radiation-induced damage to the lung parenchyma, a maximum inspiratory pressure of 40 cmH₂O or higher is sometimes required to achieve an adequate tidal volume.

Anesthesia management for each stage of surgery

Dissection and resection of the recipient's lung

In cases of severe pleural adhesions, massive bleeding may occur during pleural dissection and pneumonectomy, and attention should be paid to possible damage to the phrenic nerve and recurrent laryngeal nerve. When the lower pulmonary ligament is cut, the ipsilateral PA is temporarily ligated while contralateral pulmonary ventilation is maintained, and hemodynamic changes are observed to determine ECLS. A left-sided DLT is primarily used in lung transplantation, and the initiation of one-lung ventilation increases intrapulmonary shunt, which may aggravate hypoxemia, hypercarbia, and acidosis. Even if a ventilation strategy that allows hypercapnia is used to maintain cardiovascular stability by reducing dynamic hyperinflation and auto-positive end-expiratory pressure, the use of a buffer to maintain proper blood pH should be considered [27].

PA clamping may help to reduce the shunt but cause hypotension from a decreased RV preload and increased RV afterload. The RV preload can be improved by administering fluids, and the afterload can be improved by applying pulmonary vasodilators. To reduce PVR, 100% oxygen can be used to reverse hypoxic pulmonary vasoconstriction, or selective pulmonary vasodilators such as nitric oxide and prostaglandin I₂ can be used [18,28,29]. If hemodynamic instability occurs despite the use of ventilators and vasodilators, ECLS is necessary. Since CPB requires systemic anticoagulation, the amount of bleeding is larger than that with ECMO, and the risk of PGD may increase [30,31]. ECMO can also be used in the presence of postoperative graft dysfunction.

Donor lung anastomosis

Cold saline or ice minimizes warm ischemic injury to the transplanted lung and can cause a patient to become hypothermic. Bronchial anastomosis is followed by PA anastomosis and pulmonary vein anastomosis. When the pulmonary vein is connected to the recipient's left atrium, it is temporarily clamped using forceps, which can lead to arrhythmias, LV filling, and coronary artery occlusion. Therefore, appropriate vasopressor and fluid therapy are warranted, and care should be taken not to cause pulmonary edema during fluid therapy. Severe hemodynamic instability can occur during one-lung ventilation and PA ligation, which is due to right heart failure from a decreased RV preload and increased RV afterload. Therefore, it is necessary to administer fluid, maintain the preload, and use a pulmonary vasodilator to reduce the afterload.

During anastomosis of the transplanted lung, ECLS such as CPB or ECMO can be applied to facilitate free surgical manipulation and maintain hemodynamic stability. Veno-arterial ECMO enables fewer transfusion reoperations and less PGD in comparison to CPB [32]. In addition, CPB requires full heparinization to maintain an activated clotting time >480 seconds. However, veno-arterial ECMO can be maintained at an activated clotting time of 160–200 seconds and used instead of CPB because there is no venous reservoir and there are few blood-activating surfaces [33].

Reperfusion

At the end of left atrium anastomosis, the lungs should be inflated with a pressure of 15–20 cmH₂O and some PA clamping should be loosened to remove air from the transplanted graft. After left atrium anastomosis is completed, the ligation is released, and hypotension may occur for various reasons. Massive bleeding or myocardial stunning can be caused by cold venous return containing pulmoplegic compounds and ischemic metabolites to the left atrium. At this time, a small dose of adrenaline or calcium can be

injected. Since the right coronary artery is superiorly located, the risk of air embolism is higher. Although there is descent of the ST segment on electrocardiography, it is usually transient and lasts less than 15 minutes.

In addition, dysfunction of the new endothelium may occur due to mechanical shear stress during reperfusion, increasing microvascular permeability and pulmonary edema, which are known to be important causes of PGD (Table 3) [34,35]. This ischemia/reperfusion injury can be attenuated by slowly increasing pulmonary circulation while slowly reducing ECMO blood flow [36,37]. After reperfusion, the bronchial anastomosis should be checked using a fiberoptic bronchoscope, and RV function and vascular anastomosis should be confirmed by TEE (Figs. 1, 2).

Since the risk of right heart failure is high, the RV afterload should be reduced, and coronary perfusion should be maintained with appropriate inotropes and vasopressors. The commonly used inotropes and vasopressors are milrinone, noradrenaline, and inhaled nitric oxide, and a selective PA vasodilator can reduce PVR. Efforts must be made to correct acidosis, hypoxia, hypercapnia, and hypothermia and lower the ventilatory inspiratory pressure as much as possible [38].

A high fraction of inspired oxygen after reperfusion is associated with PGD [39]; thus, it should be kept at a low enough level to keep arterial oxygen partial pressure above 70 mm Hg [40]. To reduce damage to the transplanted lung, the peak inspiratory pressure should be kept low (15–20 cmH₂O), the positive end-expiratory pressure should be approximately 5 cmH₂O, and the respiratory rate should be maintained at 8–10 breaths per minute (Table 4) [39,40]. When transplantation is complete, the DLT should be replaced with a single-lumen ETT using a tube exchange catheter with direct or video-laryngoscopy because airway edema may occur.

Table 3. The International Society for Heart and Lung Transplantation primary graft dysfunction definition and grading [35]

Grade	PaO ₂ /FiO ₂	Radiographic infiltrates
0	>300	Absent
1	>300	Present
2	200–300	Present
3	<200	Present

PaO₂, partial pressure of oxygen in arterial blood; FiO₂, fraction of inspired oxygen.

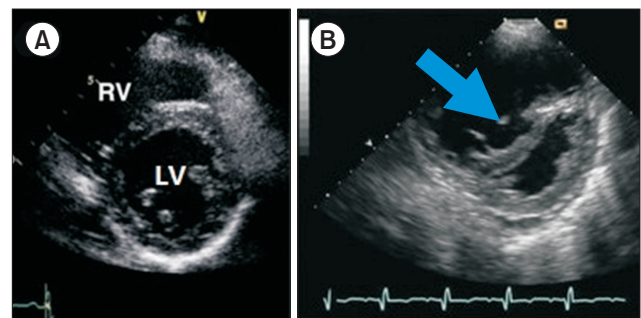


Fig. 1. Echocardiographic view. (A) Normal and (B) transgastric views show a severely dilated right ventricle (RV) with shift of the interventricular septum toward the left ventricle (LV) (arrow).

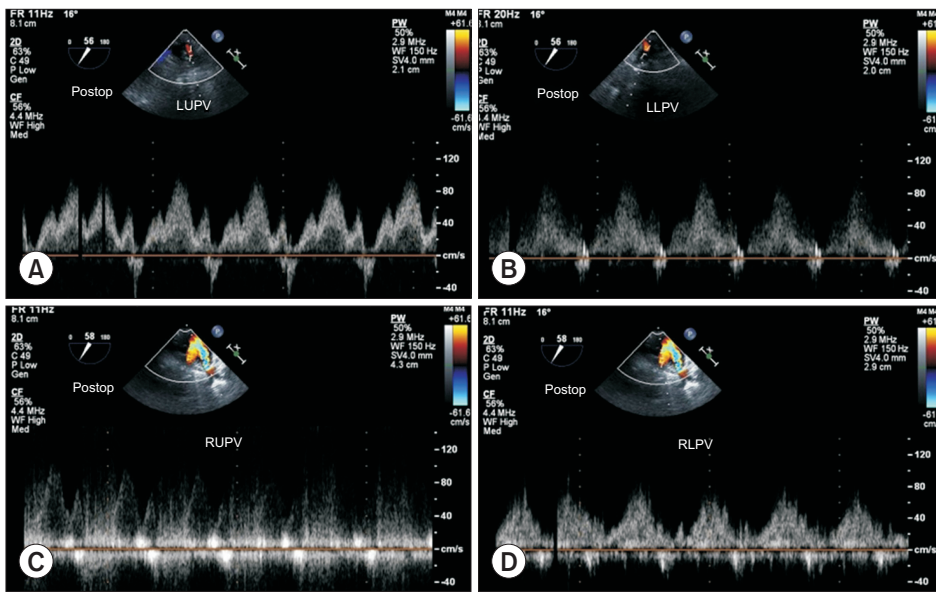


Fig. 2. Mid-esophageal view of the pulmonary vein with pulsed-wave Doppler displaying peak velocities less than 80 cm/sec. (A) Left upper pulmonary vein (LUPV), (B) left lower pulmonary vein (LLPV), (C) right upper pulmonary vein (RUPV), and (D) right lower pulmonary vein (RLPV). Postop, postoperative.

Table 4. Recommendations for intraoperative mechanical ventilation of the transplanted lungs

Recommendations
- Tidal volume of 6 mL/kg IBW. Adjust for OLV, if needed. Consider using donor body weight if the allograft is undersized
- PEEP 6 to 8 cmH ₂ O
- PIP less than 30 cmH ₂ O
- Careful recruitment maneuvers
- Lowest FiO ₂ to maintain PaO ₂ ≥70 mm Hg
- Normocapnia or low levels of permissive hypercapnia (if it allows for low tidal volume and is not associated with acidosis)
- Bronchoscopic airway clearance

IBW, ideal body weight; OLV, one-lung ventilation; PEEP, positive end-expiratory pressure; FiO₂, fraction of inspired oxygen; PaO₂, partial pressure of arterial oxygen; PIP, peak inspiratory airway pressure.

Fluid administration

Since the transplanted lung is not connected to the lymphatic system, the alveolar fluid clearance is impaired [41]; thus, fluid administration and overload can create pulmonary edema. Geube et al. [42] showed that an increased fluid volume was strongly associated with severe PGD. In their study, grade 3 PGD occurred in 25% of patients, and the odds for grade 3 PGD per each liter of intraoperative fluid increased by approximately 22%. In addition, patients with grade 3 PGD received larger volumes of red blood cell transfusions than patients without grade 3 PGD, while non-blood components (colloids and crystalloids) were not associated with grade 3 PGD. The Lung Transplant Outcomes Group also found that transfusing more than 1 L of red blood cells doubled the incidence of PGD [39]. Therefore, caution is required when correcting for hemoglobin, coagulation, and fluid losses.

Conclusion

In patients undergoing lung transplantation, there are various critical moments pertaining to anesthesia, such as anesthesia induction, one-lung ventilation during dissection, PA ligation, and reperfusion of the transplanted lung. Successful anesthesia management requires a multidisciplinary approach, including assessments of preoperative lung and cardiac function, one-lung ventilation and post-reperfusion protective ventilation strategies, the maintenance of hemodynamic stability with TEE, and the use of inotropes, vasopressors, and inhaled nitric oxide to improve hemodynamic stability, oxygenation, and ventilation of the transplanted lung. Therefore, anesthesiologists must have expertise in TEE, ECMO, and cardiopulmonary anesthesia and understand the pathophysiology of end-stage lung disease and the drugs used. In addition, communication among anesthesiologists, surgeons, and perfusionists during surgery is important for optimal patient results.

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Conflict of interest

No potential conflict of interest relevant to this article was reported.

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