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Review

Anesthetic considerations for lung transplantation

Young Chul Yoo

Department of Anesthesiology and Pain Medicine, Yonsei University College of Medicine, Seoul, Korea

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Corresponding author
Young Chul Yoo, M.D., Ph.D.
Department of Anesthesiology and Pain Medicine, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea
Tel: 82-2-2228-4440
Fax: 82-2-2227-6517
E-mail: seaoyster@yuhs.ac
ORCID
https://orcid.org/0000-0002-6334-7541

Since the first lung transplantation, developments in surgical techniques, immunosuppressants, preservation solutions, monitoring devices, anesthetic agents, and drugs and devices for hemodynamic support have resulted in improved survival rates after lung transplantation. Lung transplantation is a high-risk procedure and end-stage lung disease is frequently accompanied by compromised cardiopulmonary function. Therefore, a highly trained cardiothoracic anesthesiologist is required during the procedure. As various factors related to anesthesia may have important effects on the prognosis of the patient after the lung transplantation, an anesthesiologist must not only be familiar with the use of various medications and monitoring devices, but also understand the patient's pathophysiology and the surgical procedure.

Keywords: Anesthesia; Intraoperative care; Lung transplantation; Reperfusion injury.

INTRODUCTION

Lung transplantation is the only treatment option for end-stage lung disease (ESLD) that cannot be effectively managed using non-surgical treatment [1]. Human lung transplantation was performed for the first time in 1962 by Hardy et al. [2]. However, successful lung transplantation was first achieved in 1983 aided by advances in many fields such as immunosuppression, organ preservation techniques, and anesthetic methods [3]. Since then, lung transplantation is being performed frequently. According to the annual report of the International Society for Heart and Lung Transplantation, 64,803 adult lung transplantations were performed until June 2017, and over 4,500 lung transplantations were performed in 2016 [4]. In Korea, since the first lung transplantation in 1996, 640 lung transplants have been carried out until 2019, and more than 90 lung transplants have been performed annually since 2016. Although the number of patients receiving organ transplantation is constantly rising, organ donation is always insufficient compared to the number of patients waiting for transplantation. With a change in the society's perception of organ donation, more people are agreeing to donate their organs after death. However, in most of the brain-dead patients, the brain death is caused by head damage or cerebral hemorrhage. Unfortunately, such cases are often accompanied by pulmonary parenchymal damage. Therefore, only 15–20% of the lungs from the brain-dead donors are suitable for lung transplantation [5,6]. The utilization rate is lower than 15% in Korea. The shortage of donated organs is expected to improve with recent legal approval of living-donor lung transplantation. However, in many countries where living-donor lung transplantation has already been approved, shortage of donated lungs is still encountered.

INDICATIONS FOR LUNG TRANSPLANTATION

The primary purpose of lung transplantation is to alleviate dyspnea and to improve quality of life in patients with ESLD. While deciding whether to perform lung transplantation, it is important to make a judgment regarding the timing of the transplantation, considering the underlying disease and

its progression. The timing of the recommendation of lung transplantation to the patient is not determined by a single factor but is decided based on a comprehensive consideration of several factors such as the severity of infection, admission frequency, oxygen demand, level of carbon dioxide in the bloodstream, pulmonary function, exercise capacity, pulmonary arterial pressure, and New York Heart Association Functional Classification [7]. Patients with chronic respiratory diseases showing functional problems and patients whose survival is predicted to be less than 1–2 years without transplantation should be referred to a lung transplant specialist. After the need for lung transplantation has been determined, the patient needs several necessary tests and should wait for a certain period before the transplantation. Therefore, a decision about whether to transplant should be made before the condition of the patient deteriorates further. There are four major types of diseases that may require lung transplantation: chronic obstructive pulmonary disease (COPD), inflammatory lung diseases such as bronchiectasis, lung parenchymal diseases that may be caused by pulmonary fibrosis or chemotherapy, and primary or secondary pulmonary arterial hypertension caused by complications of congenital heart disease [8]. Although COPD is the most common indication for lung transplantation worldwide, the most common reason for lung transplantation in Korea is idiopathic pulmonary fibrosis (IPF), followed by lymphangioleiomyomatosis, COPD, and primary pulmonary hypertension [8]. Until 2018, only the lungs procured from brain-dead patients were allowed to be transplanted in Korea, and procuring lungs such as liver or kidney from the living body was forbidden. Improvements in this scenario are expected due to the recent legal approval. However, till date, nearly all the transplanted lungs have been procured from a brain-dead donor. The standard lung donor criteria are listed in Table 1 [9].

Table 1. Standard Lung Donor Criteria

Donor criteria
Age < 55 years
ABO compatibility
Clear chest radiograph
PaO_2/FiO_2 ratio > 300 mmHg, with PEEP 5 cmH_2O
Cigarette smoking history of < 20 pack-years
Absence of significant chest trauma
No evidence of aspiration or sepsis
No prior thoracic surgery on side of harvest
Absence of organisms on sputum Gram stain
Absence of purulent secretions and gastric contents at bronchoscopy
Negative for HIV antibody, hepatitis B surface antigen, and hepatitis C antibody
No active or recent history of malignancy (excluding localized squamous or basal cell skin cancer, localized cervical cancer, and primary brain tumors with low metastatic potential and in the absence or invasive procedures to the brain and skull)
No history of significant chronic lung disease

PaO_2: partial pressure of oxygen, FiO_2: fraction of inspired oxygen, PEEP: positive end-expiratory pressure, H_2O: water, HIV: human immunodeficiency virus.

PROGNOSIS AFTER LUNG TRANSPLANTATION AND CURRENT STATUS IN KOREA

The median survival time for adult lung transplant recipients was reported to be 5.6 years. However, the median survival time was 7.9 years in patients who survived for more than one year. Thus, the complications and the mortality rate were higher in the first year after transplantation [10]. The survival rate after lung transplantation in Korea is lower than that reported by the International Society for Heart and Lung Transplantation. The reason for this may be the lack of surgical experience of lung transplantation in Korea. Another reason may be that the patients had undergone the lung transplantation after their condition had deteriorated. With the increase in the number of the lung transplantations in Korea and with the surgery being carried out before worsening of the patients' condition, the survival rate after lung transplantation became similar to that at the global level [8]. Globally, the survival rate after lung transplantation has remained almost unchanged in recent years, despite many advances in the related fields.

The one-year mortality rate of 20–30% after lung transplantation is usually due to failure of lung function. Postoperative primary graft dysfunction (PGD) is known to be closely associated with ischemia/reperfusion injury and a potent activation of inflammation [11]. A recent cohort study reported that the incidence of PGD (partial pressure of oxygen [PaO_2]/fraction of inspired oxygen [FiO_2] ratio less than 200) was 16.8% during the first 72 h after lung transplantation [12]. According to this study, pulmonary arterial hypertension before the surgery was a strong independent risk factor for the PGD, and the PGD was closely associated with mortality within one year after surgery. PGD manifests in the form of acute lung injury

(ALI). Oxidative stresses play an important role in the development of ALI. Moreover, one-lung ventilation (OLV) during the lung transplantation induces ventilation perfusion mismatch, which leads to hypoxic pulmonary vasoconstriction (HPV), a defensive mechanism of the body. HPV is known to be closely related to oxidative stress [13]. Oxidative stress is increased by reperfusion of the transplanted organs as well as by OLV, mechanical ventilation, and surgical trauma. These factors play an important role in the prognosis after surgery along with the inflammatory reaction during the lung transplantation [13,14]. Impaired cardiopulmonary function of the patient may cause difficulties during the administration of anesthesia. In addition to managing these difficulties, controlling pulmonary hypertension, oxidative stress, and inflammation during surgery is also an important part of the anesthetic care. More profound anesthesia is needed as it could have an important effect on prognosis.

PREOPERATIVE EVALUATION

Evaluation of the patient should be performed focusing on several factors including pulmonary, cardiac, psychological, infectious, nutritional, and social aspects. Participation and cooperation of a multidisciplinary team is essential for preoperative evaluation. The patients who are listed to receive lung transplantation often have to wait for a long time after the listing. Condition of the patient may worsen rapidly during this period, therefore, reexamination of the patient's current condition should be carried out if necessary. The pulmonary reservoir of the patient can be predicted by arterial blood gas analysis and pulmonary function. A ventilation-perfusion (V/Q) scan can accurately predict whether the patient can tolerate OLV during operation. If the perfusion of the non-operative lungs is less than 40% on the V/Q scan, hypoxemia may be aggravated during OLV. Refractory hemodynamic instability may also occur after clamping of the pulmonary artery of the operative lung. A thorough review of the cardiac function and the degree of pulmonary hypertension is also essential. Pulmonary hypertension is considered an important independent risk factor that influences the prognosis of patients after lung transplantation [12]. It is known that pulmonary hypertension may develop with disease progression in various lung diseases that lead to ESLD [15]. Prevalence of pulmonary hypertension was close to 84% in the cases with IPF [16,17], which is the most common reason for lung transplantation in Korea. It has been reported that the mean pulmonary arterial pressure increases to more than 20 mmHg in about 90% of the end-stage COPD patients [18]. Since the right ventricle (RV) is much more vulnerable to pressure overload than the left ventricle (LV), RV function can be impaired in ESLD patients with pulmonary hypertension. RV hypertrophy is easily accompanied by pressure overload to overcome afterload [19]. RV function can be estimated by several indicators such as myocardial performance index (MPI), systolic wave velocity (S'), isovolumic relaxation time (IVRT), and tricuspid annular plane systolic excursion (TAPSE) using echocardiography. MPI can be measured from tissue Doppler imaging. MPI can be calculated by the formula (isovolumic contraction time + isovolumic relaxation time)/ejection time. When the heart rate is < 70 or > 100 beats per minute, the MPI should be corrected. S' is the velocity of the lateral annular movement during systole and can be measured from tissue Doppler imaging. IVRT is the time between closure of the pulmonary valve and opening of the tricuspid valve. It can be measured from tissue Doppler imaging of RV free wall. TAPSE is the total excursion of the tricuspid annulus between the highest position and the peak descent and can reflect RV longitudinal function. TAPSE can be measured using M-mode from the four-chamber view. Table 2 shows the interpretation of these parameters [20]. It is known that in 4–25% of patients, IPF is accompanied by coronary artery disease. Some studies have suggested that IPF-induced pro-inflammatory status is associated with an increased incidence of cardiovascular disease [21]. Therefore, coronary angiography should be performed before the lung transplantation. It is especially important in Korea where IPF is a major reason for lung transplantation. It is estimated that 50–85% of IPF patients have gastroesophageal reflux. Patients with gastroesophageal reflux require

Table 2. RV Functional Measurement

Parameter	Normal	Intermediate	Abnormal
RV MPI	< 0.28	0.28–0.32	> 0.32
S' wave of tricuspid annulus ($cm.s^{-1}$)	> 12	11.5–12	< 11.5
IVRT (s)	< 75		≥ 75
TAPSE (ms)	≥ 20	16–20	< 16

RV: right ventricle, MPI: myocardial performance index, S' wave: systolic wave, IVRT: isovolumic relaxation time, TAPSE: tricuspid annular plane systolic exertion.

medical or surgical treatment prior to the transplantation because of the increased risk of aspiration after transplantation [22].

MONITORING

Currently, there is no consensus guideline for intraoperative monitoring during lung transplantation. However, most centers routinely use transesophageal echocardiography (TEE), pulmonary arterial catheter (PAC), and arterial line in addition to standard monitors. The insertion of the arterial line should be performed prior to induction to quickly detect the hemodynamic changes during induction and to perform rapid intervention. The role and importance of TEE monitoring during lung transplantation is increasing. The anesthesiologist can detect the change in RV and LV function through TEE monitoring. It helps the decision-making regarding weaning of extracorporeal membrane oxygenation (ECMO) after surgery when ECMO is used for hemodynamic support in lung transplantation. Even when the operation is performed without ECMO, it can provide important information to help decide whether to insert ECMO for hemodynamic support during surgery. TEE also plays an important role in distinguishing the cause of hypoxemia after reperfusion. Clogging, kinking of the vessel, and narrowing of anastomosis can be ruled out if pulmonary vessel flow is confirmed through TEE. If the minimum diameter of the pulmonary artery anastomosis is greater than 75% of the diameter of the proximal pulmonary artery and if the color flow Doppler flows through the anastomosis without obstruction, the pulmonary artery anastomosis is regarded as normal [23]. In the absence of obstruction of pulmonary vessel flow, acute graft rejection or reperfusion injury can be suspected. The air originating from the donated lung often enters the systemic circulation after reperfusion. Early detection of the regional wall motion abnormality is possible with TEE. It can also find out the cause of the abnormality by confirming the presence of air in the left atrium and the LV. PAC is useful for monitoring the continuous cardiac output and the mixed venous saturation. Some centers insert the PAC before induction due to severe pulmonary hypertension and compromised right heart function. However our center prefers placing the PAC after intubation because most patients can't tolerate the supine head-down position for the whole duration of the procedure. We routinely use cerebral oximetry for early detection of cerebral hypoxia and devices such as bispectral index monitor for assessing the depth of anesthesia. As hypothermia can increase the pulmonary vascular resistance (PVR) and the chances of bleeding and infection, monitoring and maintenance of body temperature are essential [24,25]. As pulse oximetry is inaccurate under ECMO or cardiopulmonary bypass (CPB), the adequacy of oxygenation should be judged synthetically through the results of mixed venous oxygen saturation, cerebral oximetry, and arterial blood gas analysis, in addition to pulse oximetry.

INDUCTION OF ANESTHESIA

Induction is the most critical phase in anesthetic management. Despite adequate preoxygenation, desaturation progresses very quickly because of the lowered respiratory reserve in patients receiving lung transplants. Rapid desaturation and hypercarbia can rapidly increase the PVR, which may result in RV failure, especially in patients with impaired RV function [26]. Moreover, suppression of sympathetic nervous system, decrease in systemic vascular resistance, myocardial depression by anesthetics, reduction of venous return, and increase of RV afterload by positive pressure ventilation may cause severe hemodynamic compromise. Therefore, ECMO or CPB should be kept ready for an emergency. The surgeon and the perfusionist should also be involved in the induction [27]. Midazolam, etomidate, propofol, and ketamine as hypnotics, and fentanyl and sufentanil as analgesics can be used as induction agents. The choice of the anesthetic agent and the determination of its dose for induction must be tailored to the patients' condition. Lung transplant surgery requires a double lumen tube (DLT) similar to the other lung operations. Left-sided DLTs are preferred to right-sided ones because they are easier to mount and the bronchial tip of left-sided DLT does not interfere with the bronchial anastomosis [28]. If the patient has a difficult airway, initial DLT intubation can be very dangerous. In such cases, it is better to place a single lumen tube first and then replace it with DLT using a tube exchanger. In our center, we perform femoral artery cannulation in addition to right radial artery cannulation for monitoring of systemic arterial pressure, the PAC insertion for monitoring of pulmonary arterial pressure, followed by the TEE insertion.

HEMODYNAMIC AND RESPIRATORY SUPPORT DURING LUNG TRANSPLANTATION

After induction of anesthesia, ECMO or CPB is performed for hemodynamic and respiratory support during lung transplantation for the patients with moderate to severe pulmonary hypertension or RV dysfunction. In Korea, IPF is the most common reason for lung transplantation and is commonly accompanied by pulmonary hypertension. Hence, our center has routinely applied ECMO or CPB during surgery. Although CPB has been the standard technique for intraoperative cardiorespiratory support during the lung transplantation [29], results of various studies indicate that veno-arterial (VA) ECMO can be used as a substitute for CPB to provide intraoperative hemodynamic and respiratory support. Use of ECMO is associated with lower heparin doses and reduced blood activating surfaces due to lack of a venous reservoir and additional suction lines [30]. Thus, when compared with CPB, coagulopathy and inflammatory cascades are better attenuated when ECMO is used. ECMO can easily be extended to postoperative care (during postoperative graft dysfunction) [30]. Since these advantages result in better outcomes [31], some European and North American centers have changed their primary intraoperative cardiopulmonary support technique from CPB to ECMO [30,32–35]. Since 2013, our center has performed lung transplantations using the peripheral VA ECMO technique [36].

MAINTENANCE OF ANESTHESIA

For maintenance of anesthesia, inhalation agents or propofol can be used with narcotic analgesics such as sufentanil or fentanyl. Although halothane induces HPV in a dose-dependent manner, recent inhalation agents are not associated with HPV at concentrations used in lung transplantation [37]. In a recent systematic review comparing inhalation agents and intravenous anesthetics in patients undergoing OLV, no significant difference was found in the outcomes between the two types of drugs used for anesthesia [38]. However, OLV with patient's native lung may negatively influence the uptake of an inhalation agent. Hence, total intravenous anesthesia (TIVA) may be more reliable in such cases. Recently, our center changed the maintenance protocol from balanced anesthesia (sevoflurane with sufentanil) to TIVA (propofol with sufentanil).

During the surgical procedure, OLV with native lung may cause hypoxemia, hypercarbia, acidosis, and increase in PVR, which, in turn, may result in hemodynamic instability and RV failure. Therefore, appropriate ventilation strategy for OLV and hemodynamic and respiratory support using ECMO are essential. Increasing the positive end-expiratory pressure (PEEP) in the ventilated lung improves oxygenation by diverting the blood flow to the non-ventilated lung. However, slow titration is required in such cases [39]. Hyperinflation of the alveoli may increase the RV afterload and decrease the LV preload, which can result in severe hemodynamic compromise [40]. Especially, in patients with COPD or bronchiolitis obliterans syndrome, the exhalation time should be increased (inspiratory:expiratory ratio = 1:3–1:4) to minimize auto-PEEP and avoid hyperinflation [26]. If hypoxia continues during OLV, applying continuous positive airway pressure with oxygen to a non-ventilated lung can temporarily improve oxygenation until the lung is removed. In addition to its role as a salvage therapy in ESLD patients, ECMO plays an essential role in regulating hypoxemia, hypoxia, and hemodynamic instability during lung transplantation. Since our center routinely uses peripheral VA ECMO, the ventilator setting of OLV is as follows: Tidal volume is 4 ml per kg, respiratory rate is 5 breaths per minute, the FiO_2 for native lung is 1.0, and the FiO_2 for new lung after reperfusion is 0.21. Due to the nature of the peripheral VA ECMO, differential hypoxia may occur in the proximal ascending aorta, even when the estimated full flow is maintained [41]. Based on the gas analysis results from the right radial artery, the ventilator setting is adjusted to maintain the PaO_2 above 70 mmHg [41].

The ECMO protocol at our center is as follows. Before the initiation of the ECMO cannulation, a single, unfractionated heparin bolus targeting an activated clotting time between 150–180 s is administered. VA ECMO using the Bioline heparin-coated Quadrox PLS circuit system primed with 0.8 L acetated Ringer's solution is performed with femoral artery-femoral vein cannulation. An arterial cannula (15–17 Fr) for the arterial inflow is inserted into the common femoral artery via the percutaneous route using the cut-down method, followed by insertion of a cannula (20–24 Fr) into the common femoral vein for the venous outflow. The ECMO blood flow is maintained at an estimated full flow (50 ml/kg/min) until

the end of surgical procedure. The FiO_2 of the ECMO is maintained at 1.0 and the sweep gas rate is adjusted according to the arterial partial pressure of carbon dioxide from the arterial blood gas analysis, which is around 40 mmHg.

Phosphodiesterase (PDE) 3 inhibitor (milrinone), PDE 5 inhibitor (sildenafil), prostacyclin analogue (iloprost), and nitric oxide are known to decrease PVR and pulmonary artery pressure and to improve RV function [42–44]. At our center, 0.5 μg/kg/min of milrinone is infused routinely in all patients after induction, and 20 μg of iloprost mixed with normal saline (total 5 ml) is inhaled to each lung using an ultrasonic nebulizer for 20 to 30 min after reperfusion of each lung. A recent study has shown that intraoperative inhaled iloprost could prevent primary graft dysfunction and early post-transplant morbidity in patients after lung transplantation [45].

As the lymphatic drainage is disrupted in the transplanted lungs, the alveolar fluid clearance is also impaired [46]. Therefore, the transplanted lung is very sensitive to fluid administration. Fluid overload can cause pulmonary edema in such cases. Disruption of lymphatic drainage is also known to be one of the important pathophysiological mechanisms of PGD [46]. In a recent cohort study, increased fluid volume during surgery has been reported to be strongly associated with severe form of PGD [47].

MANAGEMENT AFTER REPERFUSION

Reperfusion is one of critical steps during lung transplantation. During reperfusion, the preservation solution filled in the donated lung is washed out and the de-airing process is performed. As sudden bleeding may occur in this process, volume replacement may be necessary [27,48]. Hypotension may also be caused by various metabolites from the donated ischemic lung after reperfusion. Some studies have reported that mannitol may be helpful as a scavenger of oxygen free radicals [49]. If the blood flow to the donated lung increases suddenly during the reperfusion process, mechanical sheer stress may be applied to the new endothelium. This leads to endothelial dysfunction, which is exacerbated by the reactive oxygen species. As a result, microvascular permeability and pulmonary edema are increased, which are known to be important causes of PGD [50]. Such an ischemia/reperfusion injury can be mitigated by gradually increasing the pulmonary circulation, which can be achieved by slowly decreasing the blood flow of the ECMO [51,52]. Although it is not known how to slow down the ECMO blood flow for weaning, slow weaning is thought to improve the prognosis of the patient with severe pulmonary hypertension.

After reperfusion, the anesthesiologist should confirm the patency of the bronchial anastomosis using a bronchoscope and the pulmonary vessel patency using the TEE. Immediately after reperfusion, ventilation of the transplanted lung should be started with low FiO_2, low tidal volume, and slow respiratory rate. The tidal volume should be increased gradually to 4–5 ml/kg depending on the ideal body weight of the donor for OLV [53] and to 6 ml/kg for double-lung ventilation [54] according to the lung protective strategy. Several studies have shown that a high FiO_2 after reperfusion is closely associated with the development of PGD [12]. Therefore, it is important to maintain the ventilation with FiO_2 as low as possible while maintaining the PaO_2 above 70 mmHg [55].

After the lung transplantation is complete, the DLT should be replaced with a single lumen tube. Since the airway after transplantation is usually edematous, it is necessary to use the exchange catheter and the direct or video-laryngoscopy together while performing the tube exchange.

CONCLUSION

Anesthesia for lung transplantation is one of the most challenging areas for an anesthesiologist. An anesthesiologist involved in lung transplantation should be familiar with the use of ECMO and TEE and should understand the surgical technique and pathophysiology of ESLD. Close cooperation with all the teams involved in the lung transplantation is essential. It is important to remember that the anesthesiologist's intraoperative management can have a significant impact on the patient's prognosis.

CONFLICTS OF INTEREST

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

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