Review

Physiologic Aspects in Human Lung Transplantation

Shinichiro Miyoshi, MD, Yoshihiko Mochizuki, MD, Sensuke Nagai, MD, Satoru Kobayashi, MD, and Norio Seki, MD

Heart-lung transplantation (HLT), followed by single lung transplantation (SLT) and subsequently bilateral lung transplantation (BLT) have been developed as treatments for patients with end-stage pulmonary diseases. Initially, SLT was limited to idiopathic pulmonary fibrosis (IPF) cases and thought to be contraindicated not only for infectious diseases, but also for non-infectious diseases, including pulmonary emphysema (PE) and primary pulmonary hypertension (PPH), based on physiologic points of view. However, SLT is now widely performed for those non-infectious diseases and most of the recipients return to a normal active life. It is quite possible that BLT is superior to SLT in terms of pulmonary function, and it has been reported that BLT is better for PE and PPH patients in regards to perioperative course, postoperative exercise capacity, and long-term survival. For those situations and because of the present scarcity of donor organs, SLT must be utilized for selected non-infectious diseases for which it is safe and effective. When a single lung is replaced for IPF, PE, and PPH recipients, different physiologic situations are produced postoperatively, the understanding of which is extremely important to achieve good results, not only in the perioperative but also in the long term. (Ann Thorac Cardiovasc Surg 2005; 11: 73–9)

Key words: idiopathic pulmonary fibrosis, pulmonary emphysema, primary pulmonary hypertension, pulmonary function

Introduction

Since the first single lung transplantation (SLT) procedure was successfully performed by the Toronto Lung Transplant Group in 1983,[1] dramatic improvements in surgical technique, organ preservation, diagnosis and treatment of acute rejection, and management of infection have been accomplished. Lung transplantation is now widely accepted as the ultimate treatment of choice for patients with end-stage pulmonary diseases.

From Department of Cardiothoracic Surgery, Dokkyo University School of Medicine, Tochigi, Japan

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Address reprint requests to Shinichiro Miyoshi, MD: Department of Cardiothoracic Surgery, Dokkyo University School of Medicine, 880, Kitakobayashi, Mibu, Tochigi 321-0293, Japan.

Initially, SLT was limited to only end-stage idiopathic pulmonary fibrosis (IPF) patients, based on physiologic and infectious points of view.[1] In order to overcome the inherent problems, *en bloc* double lung transplantation (DLT),[2] later replaced by bilateral single lung transplantation (BSLT),[3] was developed. However, SLT is now widely utilized for non-infectious diseases such as pulmonary emphysema (PE) and primary pulmonary hypertension (PPH), as well as IPF.[4]

Along with the development of recipient indications and operative procedures, an understanding of the physiologic aspects of lung transplantation has become important to achieve good results, not only in the perioperative but also in the long term. Since IPF, PE, and PPH represent restrictive, obstructive, and vascular pulmonary diseases, respectively, we reviewed reports of those kinds of cases with focus on the physiologic aspects in human lung transplantation.

Table 1. Pulmonary function data from idiopathic pulmonary fibrosis patients before and after single lung transplantation

Authors	Year	No.	FVC (%)		FEV_1 (%)		DLCO (%)	
			Before	After	Before	After	Before	After
Grossman[6]	1990	9	43±9	69±10	50±9	79±15	36±9	62±16
Miyoshi[7]	1999	15	29±11	65±9				
Haider[8]	2002	25	42	74	46	80	29	48

FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 second; DLCO: diffusing capacity

Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, and fatal interstitial lung disease. Since usual interstitial pneumonitis (UIP) is the most common histologic subtype and is generally unresponsive to steroid therapy, selected end-stage UIP patients are referred for lung transplantation. According to International Guidelines,[5] patients with a vital capacity (VC) less than 60 to 70% of the predicted value and/or diffusing capacity at less than 50 to 60% of the predicted value are considered to be functionally within the transplant window.

Preoperative pulmonary functron test (PFT) results of IPF patients who underwent SLT are shown in Table 1.[6-8] Each of those patients had a severe restrictive pulmonary disorder and poor diffusion capacity, as well as severe resting hypoxia. Thabut et al.[9] reported that arterial blood gas data in room air were 45.0 mmHg (38.0-51.0 mmHg) for PaO_2 and 45.0 mmHg (41.0-50.0 mmHg) for $PaCO_2$ in 28 IPF patients. They also investigated the preoperative pulmonary hemodynamic status of those cases obtained by right heart catheterization and found that the systolic, diastolic, and mean pulmonary artery (PA) pressures were 41.0 mmHg (36.0-55.0 mmHg), 20.0 mmHg (15.0-25.0 mmHg), and 28.0 mmHg (25.0-35.0, mmHg), respectively, while the cardiac index was 3.2 L/minute (2.8-3.7 L/minute). They concluded that patients with severe pulmonary hypertension (mean PA pressure>40 mmHg) were contraindicated for lung transplantation.

IPF patients were initially selected as ideal candidates for SLT by the Toronto Lung Transplant Group.[1] One of the reasons given was physiologic, as poor compliance and increased pulmonary vascular resistance by the native lung would ensure that ventilation and perfusion were directed preferentially toward the transplanted lung, thus avoiding a ventilation-perfusion imbalance. As expected, relative perfusion to the transplanted lung was 63±14% of total perfusion after 3 postoperative days, 73±9% after 1 month, and 77±7% at 3 months after transplantation.[6] Postoperative ventilation scintigraphy results have also demonstrated that 80% of total ventilation was shifted to the transplanted lung in patients at 29±16 months after the procedure.[7]

PFT results after SLT in the patients shown in Table 1 were significantly improved, however, those following a SLT typically demonstrate mild restrictive and diffusion disorders, because of the remaining native lung. When PFT results were compared between SLT and BSLT, there were no significant differences found according to the type of transplant.[10]

A rapid improvement in exercise tolerance as measured by a 6-minute walk test was apparent within 3 to 6 months after transplantation, and tolerance stabilized thereafter.[6] Another report found that maximal oxygen consumption ($\dot{V}O_2max$) was closely correlated with postoperative VC in SLT recipients,[7] and a later study reported that there was no significant difference in exercise tolerance between SLT and BSLT patients.[10]

Since postoperative VC remains subnormal and is one of the limiting factors for postoperative exercise capacity,[7] donors for SLT should be selected with the aim that post-transplant VC becomes as large as possible. Factors influencing post-transplant VC can be investigated by comparison of post-transplant VC with the predicted normal VC of the donor and recipient. Our previous studies[7,11] demonstrated that post-transplant VC in the recipient was closely correlated with the predicted normal VC in the donor following left SLT, and that there was no correlation between post-transplant VC and predicted normal VC in the recipient. These findings can be explained by the fact that the left hemithorax of SLT recipients with IPF readily accommodates a relatively large donor lung by a descent of the diaphragm to a more normal position and a shift in the mediastinum toward the right side. Thus, using such a procedure, a larger thoracic volume than normal is supplied for the allograft in a left SLT.

In contrast to a left SLT, we found no correlation between post-transplant VC in the recipient and predicted

normal VC in the donor in right SLT cases, though there was a tendency for correlation between post-transplanted VC and predicted normal VC of the recipient. Further, post-transplanted VC was the same or smaller than predicted normal VC in the recipient, which suggested that post-transplant VC is limited by the normal right hemithoracic volume in the right SLT and not by the transplant donor lung volume. The right hemithorax, which is shrunken prior to transplantation, may return to the normal position without a shift of the mediastinum or descent of the diaphragm.

When selecting a donor to obtain a post-transplant VC value that is as large as possible, the predicted normal VC of the donor should be larger than that of the recipient in a left SLT, while in a right SLT, the donor should be chosen so that the predicted normal VC of the donor approximates the predicted normal VC of the recipient. BSLT does not have an advantage over SLT in terms of postoperative pulmonary function and exercise tolerance. Thus, when BSLT is applied to IPF, the donor lung volumes should be matched to the recipient predicted normal lung volume, as in a right SLT.[10)]

Table 2. Pulmonary function data from pulmonary emphysema patients before and after double lung transplantation[15)]

	Before	After
VC L (%)	2.0±0.6 (56±26)	3.3±0.3 (91±10)
FEV_1 L (%)	0.5±0.2 (18±8)	2.9±0.4 (92±8)
TLC L (%)	7.2±0.5 (139±19)	4.8±0.4 (94±16)
DLCO ml/minute/mmHg (%)	5.1±1.3 (23±9)	19.0±2.4 (90±22)

VC: vital capacity; FEV_1: forced expiratory volume in 1 second; TLC: total lung capacity; DLCO: diffusing capacity

Pulmonary Emphysema

Initially, pulmonary emphysema (PE) was believed to be a contraindication for SLT, because the loss of elastic recoil in the native lung may lead to progressive air trapping in the native lung, and subsequently shift the mediastinum and cause crowding of the transplanted lung.[1)] Since perfusion would be directed toward the transplanted lung, because of the expected lower pulmonary vascular resistance, a ventilation-perfusion imbalance would be the result.[12,13)] Thus, in 1986, *en bloc* DLT was developed for PE patients,[2)] which, though complex, produced excellent results in the initial group of patients with PE for whom it was applied.[14)] Pre- and post-transplantion pulmonary function data from DLT recipients are illustrated in Table 2.[15)] Preoperative PFT results in DLT recipients demonstrated a severe obstructive abnormality, hyperinflation, and a marked reduction in diffusing capacity, though each parameter returned to normal or near normal in all following transplantation cases.

Mal et al.[16)] reported preliminary success with SLT in 2 consecutive patients with end-stage PE and, despite the persistence of an obstructive syndrome after transplantation, clinical status was good, blood gases were markedly improved, and ventilation-perfusion imbalance did not occur on lung scans. Levine et al.[17)] also reported medium term functional results, a portion of which are shown in Table 3, and significant improvement in lung function was apparent by 3 months after transplantation, while it had reached a plateau by 12 and 24 months after transplantation in that and another study.[18)] In the study of Levine et al., improvements in ventilation and perfusion occurred equally and persisted from 12 to 24 months after SLT.[17)] In another report of allograft-specific pulmonary function, the allograft lung functioned at a normal level for the recipient and did not appear to be constrained by hyperinflation of the contralateral lung.[19)] Further, exercise capacity, expressed by $\dot{V}O_2max$, at 6 months after surgery was 43±13% of the predicted value in normal subjects and became stable by 24 months after surgery.[17)]

The decision regarding the choice of SLT versus BSLT for patients with PE must be based on several considerations. Focusing on physiology, improvements in spirometry findings, oxygenation, and exercise tolerance were all better following BSLT, and the superiority was sustained during the late follow-up period,[20-22)] while other recent reports have shown that BSLT for PE and alpha-1 anti-trypsin deficiency PE resulted in better long-term survival. One of the factors for these better results may be additional pulmonary reserve in BSLT as compared to SLT recipients, which may be especially important if chronic rejection (bronchiolitis obliterans syndrome) develops.[23)]

The relationship between graft position and pulmonary function following SLT for PE is another interesting issue. Levine et al.[24)] observed that in patients who underwent a left-sided SLT, the native right lung appeared to compress the left lung graft on radiograph images, whereas the native left lung did not appear to compress the right lung graft in right-sided SLT. They hypothesized that a right SLT may provide a functional advantage over

Table 3. Pulmonary function and quantitative ventilation perfusion data from pulmonary emphysema patients before and after single lung transplantation[17]

Months	Before	After			
		3	6	12	24
Subjects (n)	22	22	22	22	10
FEV_1, L	0.49±0.13	1.71±0.43	1.75±0.39	1.58±0.52	1.45±0.53
% pred	16±4	57±12	60±12	54±18	52±19
FVC, L	1.68±0.54	2.29±0.59	2.41±0.54	2.40±0.56	2.40±0.61
% pred	43±11	58±11	62±11	62±16	66±17
Subjects (n)	15	20	18	17	8
TLC, L	7.31±1.43	6.39±1.35	6.53±1.46	6.19±1.52	6.13±0.82
% pred	132±29	109±19	106±20	107±20	115±16
DLCO	5.8±2.6	14.6±6.1	16.1±4.8	16.3±4.6	15.7±2.9
% pred	26±13	62±23	69±20	70±19	75±15
Subjects (n)	21	22	19	17	10
V (% to SLT)	51±10	84±9	85±11	84±11	81±11
Q (% to SLT)	50±8	81±10	81±8	80±9	82±7

FEV_1: forced expiratory capacity; FVC: forced vital capacity; TLC: total lung capacity; DLCO: diffusing capacity; V: ventilation; Q: perfusion; SLT single lung transplantation

a left SLT for patients with PE, and compared PFT results before and after SLT as well as quantitative ventilation-perfusion lung scan results between patients who underwent left and right SLT procedures. Additionally, they compared graded-exercise test results at 3 and 12 months following SLT between the 2 groups. Their data revealed no statistical difference in PFT results or graded-exercise test results between the 2 groups, though patients who underwent a right SLT showed greater increases in FEV_1 and forced vital capacity (FVC). They speculated that these functional advantages of right SLT over left SLT were most likely due to the larger size of the right lung. Our graft specific pulmonary function study,[7] which utilized data reported by Brunsting et al.,[19] also did not show any functional advantage of left SLT over right SLT in PE patients. However, we recommend a right SLT for recipients with PE, because the right lung is larger than the left lung (55% vs. 45%), as noted by Levine et al.[24]

Primary pulmonary hypertension

Primary pulmonary hypertension (PPH) is a pulmonary vascular disease of unknown etiology, clinically defined as pre-capillary pulmonary hypertension in the absence of congenital or acquired heart disease, thromboembolic disease, pulmonary veno-occlusive disease, primary parenchymal or interstitial disease, or collagen vascular disease.[25] Although heart-lung transplantation (HLT) was initially indicated for PPH,[26] this option remains limited mainly by the scarcity of donor organs.

Traditionally, SLT was not considered a treatment option for PPH, due to concerns that the vasculature of the transplanted lung would not able to tolerate the entire cardiac output.[26] However, animal studies and reported experiences with SLT for IPF or PE-associated pulmonary hypertension suggested that a single transplanted lung could accommodate the entire pulmonary blood flow. Thereafter, Levine et al.[27] first successfully performed SLT procedures for 3 PPH patients. Later, Pasque et al. reported 3-month hemodynamic follow-up results for SLT in patients with pulmonary hypertension.[28] The hemodynamic data for 7 patients obtained at cardiac catheterization before (mean, 61 weeks; range, 7-241 weeks) and after (mean, 13 weeks; range, 3-30 weeks) SLT are shown in Table 4. Pulmonary artery pressure, pulmonary vascular resistance index (PVRI), and central venous pressure each dropped significantly after SLT, while depressed cardiac index and right ventricular ejection fraction (RVEF) values returned to near normal. Quantitative pulmonary perfusion scintigraphy at a mean 17 weeks after transplantation demonstrated a significant ($p=0.001$) increase in perfusion to the transplanted lung from 56±6% to 89±7%. Further, there was a concomitant slight, but significant ($p=0.004$), decrease in ventilation to the transplanted side from 56±6% to 49±8%, as shown in Table 5. As expected, the majority of cardiac output was distributed to the graft, and ventilation was equally divided between the native lung and the graft, however, pulmonary edema or hypoxemia due to ventilation-perfusion imbal-

Table 4. Hemodynamic data from pulmonary hypertension patients before and after single lung transplantation[28)]

Hemodynamic parameter	Before	After
PA systolic	92±18	29±6
PA diastolic	41±6	13±8
PA mean	64±18	18±5
CVP	10±6	1±2
Cardiac index	2.54±0.98	3.54±0.70
RVEF	22±15	51±11
PVRI	1,924±663	233±73

All pressures are shown as mmHg, cardiac index in l/minute/m^2, right ventricular ejection fraction (RVEF) are shown as percentages, and pulmonary vascular resistance index (PVRI) as dyne/second/cm^{-9}. PA: pulmonary arterial; CVP: central venous pressure.

Table 5. Pulmonary ventilation and perfusion scintigraphy data from pulmonary hypertension patients before and after single lung transplantation[28)]

Ventilation scan	Before	After
Transplanted side	56±6%	49±8%
Opposite side	44±6%	51±8%
Perfusion scan	Before	After
Transplanted side	56±6%	89±7%
Opposite side	44±7%	11±7%

Values are shown as mean ± SD.

ance did not occur. After transplantation, all patients returned to the New York Heart Association functional class I or II from their preoperative level of class III or IV. These reports support the option of SLT in patients with PPH, though the long-term durability of such hemodynamic changes require further study before widespread application can occur.

Levine et al.[29)] reported on the physiologic changes that occurred during rejection of a lung graft in 2 recipients, who survived following SLT for PPH. Initially, the patients did well with unlimited exercise tolerance after transplantation, but then developed marked dyspnea on exertion and hypoxemia on postoperative days 144 and 120, respectively. Pulmonary function testing showed a marked deterioration of function, and transbronchial lung biopsy specimens revealed acute graft rejection in 1 patient and evidence of chronic graft rejection in the other. Quantitative ventilation-perfusion lung scanning demonstrated a marked decrease in ventilation to the transplanted lung (from 55 to 26%, and 48 to 35%, respectively), which was associated in both cases with only a mild decrease in perfusion (from 84 to 70%, and 91 to 81%, respectively). Although acute rejection histologically is a vascular injury, vascular resistance may continue to remain lower in the transplanted lung than that in the native hypertensive lung, resulting in a majority of the perfusion continuing to flow to the transplanted lung. In contrast, ventilation that is initially equally divided between the native and transplanted lungs following transplantation readily shifts to the native lung during rejection in PPH patients. Chronic rejection, or bronchiolitis obliterans, is pathologically a disorder of the airways and a preferential shift in ventilation is expected in this situation. The V/Q mismatch results in markedly decreased arterial oxygen saturation, widened alveolar-arterial oxygen gradients, and clinically debilitating dyspnea. The authors concluded that rejection might result in a significant V/Q mismatch and hypoxemia in PPH patients who have undergone SLT, which might limit the use of this specific type of surgery for those patients.

Chapelier et al.[30)] applied DLT to PPH patients, because of concerns with SLT and the concomitant successful development of DLT for end-stage lung disease,[31)] and compared the outcomes with those who underwent HLT and those who received an SLT. The hemodynamic outcomes in the patients who received DLT are shown in Table 6. The results demonstrated that HLT and DLT for PPH were equally effective for obtaining early and durable right-sided hemodynamic and respiratory improvements. Although the authors only performed SLT for a single PPH patient, they recommended DLT for PPH, because of the critical postoperative course and uncertain long-term results of SLT.

A Pittsburgh group[32)] retrospectively analyzed the results of 11 SLT, 22 BLT (including 4 *en bloc* DLT and 18 BSLT), and 24 HLT procedures for patients with pulmonary hypertension caused by PPH (n=27) or Eisenmenger's syndrome (n=30), with SLT, BLT, and HLT performed for 7, 12, and 8 PPH patients, respectively. Although postoperative pulmonary artery pressures decreased in all 3 allograft groups, those in the SLT recipients remained significantly higher than those in the BLT and HLT recipients. Cardiac index improved significantly in only the BLT and HLT recipients, while a significant ventilation/perfusion mismatch occurred in the SLT recipients. Further, graft-related mortality was significantly higher and overall functional recovery significantly lower after 1 year in the SLT patients, as assessed by the New York Heart Association functional class, as compared with BLT and

Table 6. Hemodynamic data from pulmonary hypertension patients before and after double lung transplantation[30]

Parameters	Before	Day 0	Day 2	After 6 months
RAP	10±3	4±2	7±4	3±1
PAP	60±8	20±5	19±5	13±4
PCWP	6±1	11±6	14±4	6±2
CI	2±0.3	3.8±1.2	3.5±0.7	3±0.6
SAP	73±10	76±7	78±8	91±16
PVR	27±3	3±2	2±1.3	2.4±2

RAP: mean right atrial pressure (mmHg); PAP: mean pulmonary arterial pressure (mmHg); PCWP: pulmonary capillary wedge pressure (mmHg); CI: cardiac index (L/minute per square meter); SAP: mean systemic arterial pressure (mmHg); PVR: pulmonary vascular resistance (Wood units).

HLT recipients. Thus, the authors concluded that BLT may be a more satisfactory option for patients with PPH and Eisenmenger's syndrome caused by simple congenital heart disease. Regarding the survival benefit in PPH recipients, Conte and colleagues[33] demonstrated that the survival for BLT at all time points up to 4 years was 100%, in contrast to 67% at 30 days and 50% at 4 years for SLT.

Following lung transplantation for severe chronic pulmonary hypertension, two interesting phenomena have been observed in the short-term postoperatively. One is right ventricular outflow obstruction, in which an acute reduction in pulmonary pressures after lung transplantation may produce a sudden decrease in cavity size of a hypertrophied right ventricle resulting in acquired right ventricular outflow tract obstruction, which can be diagnosed by transesophageal echocardiography.[34] It has been reported that stopping inotropic agents led to a dramatic improvement in hemodynamics, as evidenced by the resolution of systemic hypotension, along with decreased heart rate and right ventricular pressure.[35] The other phenomenon is left ventricular failure. Chapelier[30] reported that a transient postoperative left ventricular dysfunction was observed following DLT in 3 patients, though right ventricular function was normalized. This circumstance may be related to a compliance disorder of the small left ventricle with a paradoxic ventricular septum.

Conclusion

It is quite reasonable to state that BLT is superior to SLT for all end-stage pulmonary diseases in terms of pulmonary function. However, since the supply of donor organs is extremely limited, SLT remains an important procedure for all non-infectious diseases. When a single lung is replaced in IPF, PE, and PPH recipients, different physiologic situations are produced postoperatively. An understanding of these different physiologic aspects is extremely important to achieve good results, not only perioperatively but also in the long term.

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