

Current status and potential of living-donor lobar lung transplantation

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1. ABSTRACT

Although cadaveric lung transplantation (CLT) offers acceptable prospects for 5-year survival, chronic rejection and donor shortages remain major problems. In an effort to address the donor shortage issue, living-donor lobar lung transplantations (LDLLT) have been performed in some institutions. As of 2006, LDLLT has been performed in approximately 300 patients worldwide. The survival appears to be similar to or better than International Society for Heart and Lung Transplantation registry data on CLT. Because of the possible serious complications after donor lobectomy, LDLLT should be performed only for very sick patients by a well-prepared program. This type of procedure can be applied to restrictive, obstructive, infectious, and hypertensive lung diseases for both pediatric and adult patients who would die soon otherwise.

2. INTRODUCTION

Living-donor lobar lung transplantation (LDLLT) was pioneered by the University of Southern California (USC) group for patients who were thought to be too critical to wait for a cadaveric lung transplantation (CLT). A single donor was used in the beginning and successful living-donor single lobe transplantation has been reported. (1) However, the later experience of single lobe transplantation was not satisfactory. (2) It is for this reason that USC group has developed a bilateral LDLLT in which two healthy donors donate their right or left lower lobes (Figure 1). (3, 4)

Because only two lobes are transplanted, LDLLT seems to be best suited for children and small adults, and was initially applied most exclusively to patients with cystic

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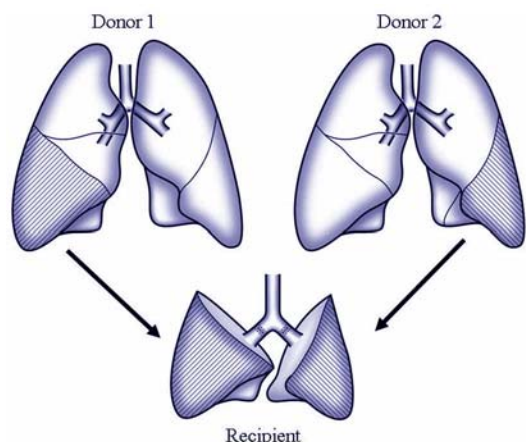


Figure 1. Bilateral living-donor lobar lung transplantation. Right and left lower lobes from 2 healthy donors are implanted in the recipient in place of whole right and left lungs, respectively.

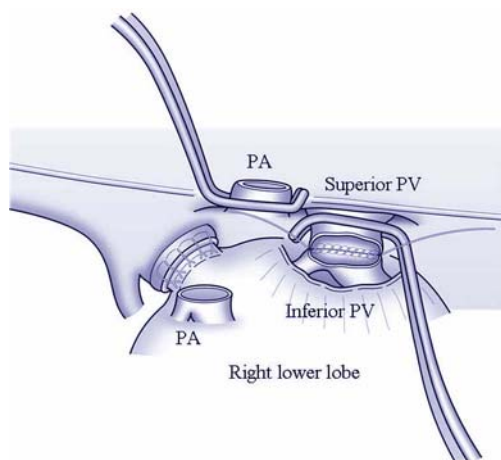


Figure 2. Right graft implantation. The bronchial anastomosis has been completed. The venous anastomosis is conducted between the donor right inferior pulmonary vein and the recipient right superior pulmonary vein using a 6-0 Prolene continuous suture.

fibrosis. (3) Recently, indications for LDLT have been expanded to include both pediatric and adult patients with various lung diseases such as idiopathic pulmonary fibrosis and primary pulmonary hypertension. (5-9) As of 2006, LDLT has been performed in approximately 300 patients worldwide. The survival rate appears to be similar to or better than International Society for Heart and Lung Transplantation (ISHLT) registry data. (10) This paper will review the current status and potentials of LDLT.

3. SURGICAL TECHNIQUE

The most commonly used procedure involves a right lower lobectomy from a larger donor and a left lower lobectomy from a smaller donor, although the side selection can be changed based on the degree of interlobar fissure development. After induction of general anesthesia, donors are intubated with a left-sided double lumen

endotracheal tube. The donors are placed in the lateral decubitus position and a posterolateral thoracotomy is performed through the 5th intercostal space. Fissures are developed using linear stapling devices. The pericardium surrounding the inferior pulmonary vein is opened circumferentially. Dissection in the fissure is carried out to isolate the pulmonary artery to the lower lobe, and to define the anatomy of the pulmonary arteries to the middle lobe in the right side donor and to the lingular segment in the left side donor. If the branches of middle lobe artery and lingular artery are small, they are ligated and divided. Intravenous prostaglandin E1 is administered to decrease systolic blood pressure by 10 to 20 mmHg. Five thousand units of heparin and 500 mg of methylprednisolone are administered intravenously. After placing vascular clamps in appropriate positions, the division of the pulmonary vein, the pulmonary artery and bronchus are carried out in that order. When the bronchial orifices of the right middle lobe and superior segment of the lower lobe arise opposite each other, a right lower lobe sleeve resection can be used. The resected lobes are flushed with preservation solution both antegradely and retrogradely from a bag held about 50 cm above the table. Lobes are gently ventilated with room air during the flush.

Recipients are anesthetized and intubated with a single lumen endotracheal tube in children and with a left-sided double lumen endotracheal tube in adults. The "clamshell" incision is used and both chest cavities are entered through the 4th intercostal space. The ascending aorta and the right atrium are cannulated after heparinization and patients are placed on standard cardiopulmonary bypass. After bilateral pneumonectomy, the right lower lobe implantation is performed followed by the left lower lobe implantation. The bronchus, pulmonary vein, and pulmonary artery are anastomosed consecutively. The venous anastomosis is conducted between the donor inferior pulmonary vein and the recipient superior pulmonary vein (Figure 2). Just before completing the bilateral implantations, 500 mg to 1 g of methylprednisolone is given intravenously and nitric oxide inhalation is initiated at 20 ppm. After both lungs are reperfused and ventilated, cardiopulmonary bypass is gradually weaned and then removed. Three surgical teams are required in LDLT and they communicate closely to minimize graft ischemic time.

4. EVALUATION AND SELECTION IN THE RECIPIENT

Patients being considered for LDLT should meet the criteria for conventional bilateral lung transplantation. Because of possible serious complications in the donor lobectomy, LDLT should be indicated only for critically ill patients who are unlikely to survive the long wait for cadaveric lungs. In our LDLT experience (n = 43), 26 patients (60%) were bed bound and 5 (12%) were on a ventilator.

Controversy exists over whether LDLT can be used on patients already on a ventilator or requiring retransplantation. The USC group reported that, among

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Table 1. Distribution of diagnoses from patients undergoing LDLLT¹

	USC ² (n = 123)	SLCH ³ (n = 38)	Okayama (n = 43)
Cystic fibrosis	84%	55%	2%
Pulmonary hypertension	4%	2%	35%
Pulmonary fibrosis	4%	—	28%
Obliterative bronchiolitis	2%	7%	16%
Lymphangioleiomyomatosis	—	—	7%
Re-transplantation	6%	31%	0%

Abbreviations: living-donor lobar lung transplantation¹, University of Southern California², St. Louis Children's Hospital³

Table 2. The eligibility criteria for living lobar lung donation

<ul style="list-style-type: none"> • Age 18-60 years and able to give informed consent • No active tobacco smoking or a significant smoking history • No active lung disease/previous ipsilateral thoracic surgery • No identifiable risk for familial lung disease (i.e. familial forms of IPF1 or PAH2) • No cachexia (BMI3 < 18 kg/m2) or obesity (BMI ≥ 30 kg/m2) • ABO blood type compatibility with recipient • Donor lobe size compatible with recipient • Normal pulmonary function and arterial blood gas results • No conditions that significantly increase the risk of general anesthesia, surgery, and postoperative recovery • No psychosocial, ethical issues, or concerns about donor motivation • Not pregnant • No active malignancy • No active significant infection (HIV, hepatitis, acute CMV)

Abbreviations: idiopathic pulmonary fibrosis¹, pulmonary arterial hypertension², body mass index³

their 123 LDLLTs, patients on a ventilator preoperatively had significantly worse outcomes, and those undergoing retransplantation had an increased risk of death. (11) The St. Louis group reported that LDLLT (n = 13) provided better survival than conventional CLT (n = 26) for retransplantation. (12, 13) We have successfully performed LDLLT for all 5 patients who had been on a ventilator for as long as 7 weeks. (14)

In the USA, the indications for LDLLT continue to be dominated principally by cystic fibrosis (Table 1). (11-13) The distribution of diagnoses was quite unique to Japan where cystic fibrosis is a very rare disease. (14) Different indications, such as primary pulmonary hypertension and idiopathic pulmonary fibrosis were frequently found in patients receiving LDLLT. In 7 patients with obliterative bronchiolitis in Okayama, five were after bone marrow transplant for leukemia (n = 4) and for aplastic anemia (n = 1), one was after Steven-Johnson syndrome, and one was secondary to ingestion of Sauropus androgynus. (15) We have accepted patients with various lung diseases including hypertensive, restrictive, obstructive, and infectious lung diseases.

5. DONOR SELECTION AND SIZE MATCHING

Potential donors should be competent, willing to donate free of coercion, medically and psychosocially suitable, fully informed of the risks and benefits as a donor, and fully informed of risks, benefits, and alternative

treatment available to the recipient. Although immediate family members (relatives within the second degree or a spouse) have been the only donors in our institution, other institutions have accepted extended family members and unrelated individuals. (11, 13, 14) HLA matching is not required for donor selection. The Vancouver Forum Lung Group proposed the eligibility criteria for living lobar donation (Table 2). (16)

Appropriate size matching between the donor and recipient is important in LDLLT. It is often inevitable that small grafts are implanted in LDLLT in which only two lobes are implanted. Excessively small grafts may cause high pulmonary artery pressure, resulting in lung edema. (17) A pleural space problem may increase the risk of empyema. Overexpansion of the donor lobes may contribute obstructive physiology by early closure of small airways. (18)

We have previously proposed a formula to estimate the graft forced vital capacity (FVC) based on the donor's measured FVC and the number of pulmonary segments implanted. (6) Given that the right lower lobe consists of 5 segments, the left lower lobe of 4 and the whole lung of 19, total forced vital capacity (FVC) of the 2 grafts is estimated by the following equation.

Total FVC of the 2 grafts = Measured FVC of the right donor × 5/19 Measured FVC of the left donor × 4/19

When the total FVC of the 2 grafts is more than 45-50% of the predicted FVC of the recipient (calculated from a knowledge of height, age, and sex), we accept the size disparity regardless the recipient's diagnosis.

Total FVC of the 2 grafts / Predicted FVC of the recipient > 0.45 – 0.5

The mean graft FVC estimated by the equation was 1881 ± 48 ml (range 1455 to 2499 ml) or 66.7% (range 47.7 to 103.0%) of predicted FVC of the recipient. The recipient's mean measured FVC at six months was well correlated with the estimated graft FVC. (19) Although the amount of tolerable size discrepancy between donors and recipients is currently unknown, we reported that LDLLT can be applied to selected patients with hyperinflated lungs such as lymphangioleiomyomatosis. (20)

6. RECIPIENT OUTCOME

There are only three groups which have reported a summary of recipient outcome. The USC group recently published their ten-year experience on 123 LDLLT recipients including 39 children. (11) In their series, retransplantation and mechanical ventilation were identified as risk factors for mortality. One, 3-, and 5-year survival was 70%, 54%, and 45%, respectively. Despite the critical condition of many of these recipients, survival after LDLLT at USC was comparable with that of reported cadaveric lung transplantation from the ISHLT Registry. (10)

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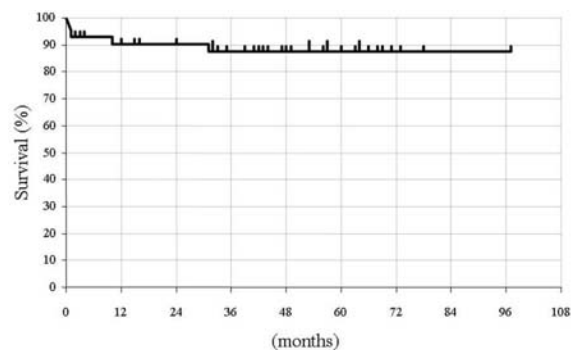


Figure 3. Survival after living-donor lobar lung transplantation at Okayama University (n = 43). Five year survival was 87.6%. There were no deaths after three years.

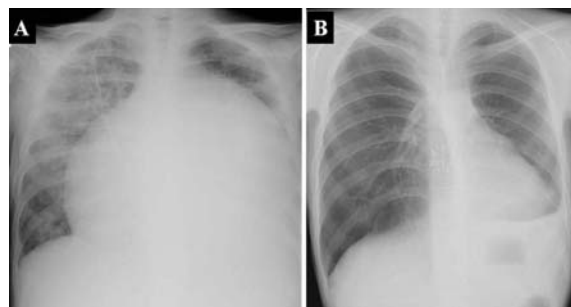


Figure 4. A 15 year old boy with primary arterial hypertension. A, pre-transplant. B, 4 months after receiving LDLT. The boy underwent LDLT with a right lower lobe from his father (48 years old) and a left lower lobe from his sister (20 years old). The height and weight was 175 cm, 60.0 kg for the recipient, 180 cm, 71.5 kg for the father, and 160 cm, 43.0 kg for the sister. Given that the right lower lobe consists of 5 segments and the left lower lobe of 4, total FVC of the 2 grafts was estimated to be 2,408 ml ($5,800 \text{ ml} \times 5/19 + 4,060 \text{ ml} \times 4/19$), or 57.6% of the recipient's predicted FVC (4,180 ml). Mean pulmonary artery pressure decreased from 52 mmHg to 15 mmHg.

SLCH (St. Louis Children's Hospital) reported similar results in 38 pediatric LDLT recipients. (13) They reported that the ratio of the predicted total lung capacity (TLC) provided to the recipient by the donor lobes to the predicted TLC of the recipient was an important prognosticator. Patients receiving lobes whose combined resultant TLC was anticipated to be equal or greater than 80% of the recipient's predicted TLC had a 5-year survival of 57% compared with 26% in those who did not. Interestingly, they recently reported that perioperative mortality of retransplantation was only 7.7% in the patients who had LDLT versus 42.3% in the cadaveric donation group. (12) We (Okayama University group) recently published institutional results in 30 LDLT recipients. (14) As of December 2006, we have accumulated LDLT experience in 43 patients including 8 children. There were three early deaths (acute rejection, Aspergillus infection and heart failure) and two late deaths (encephalitis and chronic rejection) during a follow-up period of 1-98 months. The 5-year

survival was 87.6% and there were no deaths after three years (Figure 3).

These reports from three programs with large numbers of patients suggest that survival after LDLT can be as good as or better than survival after conventional CLT. The question of whether two pulmonary lobes can provide a sufficient long-term pulmonary function and clinical outcome to recipients has been recently answered. The USC group reported that LDLT provided comparable intermediate and long-term pulmonary function and exercise capacity to bilateral CLT in adult recipients surviving more than 3 months after transplantation. (21) We have observed similar results in our LDLT recipients. FVC improved gradually after discharge and reached 77.4% of predicted, at two years. The improvement of FVC was associated with the improvement in FEV1, indicating that there was no obstructive change in the transplanted grafts. There were obvious concerns regarding whether pulmonary hypertension would develop in two lobes receiving a patient's entire cardiac output. In our LDLT recipients with pulmonary hypertension, their mean pulmonary artery pressure decreased from 62 ± 4 mmHg to 15 ± 2 mmHg at discharge, validating the functional capacity of the two lobes to handle the cardiac output of pediatric and adult recipients with pulmonary hypertension. Chest radiography demonstrated marked improvement of cardiomegaly as shown in Figure 4. Of note was that right single lobe transplantation was successfully performed in a 10 year old boy. (9) His systolic pulmonary artery pressure decreased to 32 mmHg at one year even though the transplanted lobe received 77% of the cardiac output.

7. DONOR OUTCOME

The Vancouver Forum Lung Group summarized the world experience on approximately 550 living lung donors. (16) Sixty percent of the live lung donors have been male, 76% have been related to the recipient and 24% were unrelated. There has been no reported perioperative mortality of a lung donor. Approximately 4% of live lung donors have experienced an intraoperative complication that included the necessity of a right middle lobe sacrifice. Approximately 5% of them have experienced complications requiring surgical or bronchoscopic intervention. The USC group reported that right-sided donors were more likely to have a perioperative complication than left-sided donors, probably secondary to right lower and middle lobe anatomy. (22)

While the outcomes are well investigated in the recipient, long-term outcomes of live donors have not been well documented. The Massachusetts General Hospital (MGH) group reported that mean donor FVC decreased by $14 \pm 4\%$. (23) Despite preservation of lung function within the normal range, some donors also experienced a subjective decline in exercise tolerance. Donors reported positive feelings about donation, but wished to be recognized and valued by the transplant team and the recipient.

Table 3. Comparison between LDLLT¹ and cadaveric lung transplantation

	LDLLT ¹	Cadaveric transplantation
Waiting time	short	long
Schedule	controllable	uncontrollable
Ischemic time	short	long
Graft size	small	full
Primary graft failure	infrequent	10-20%
Infection transmitted from graft	infrequent	frequent
Number of Teams	3	2
Bronchial complication	rare	5%
Chronic rejection	often unilateral	major cause of death

Abbreviation: living-donor lobar lung transplantation¹

8. COMPARISON WITH CADAVERIC LUNG TRANSPLANTATION

Advantages and disadvantages of LDLLT compared to conventional CLT are summarized in Table 3. The current availability of cadaveric donor lungs has not been able to meet the increasing demand of potential recipients in most counties. The average waiting time for a cadaveric lung is about 3 years in Japan. In contrast, LDLLT can be scheduled and performed within a few days during which donor evaluation and informed consent can be done.

In general, the ischemic time for LDLLT is much shorter than CLT. In our experience, the ischemic time of the right graft was 158 ± 6 minutes and that of the left graft was 113 ± 5 minutes. Despite improved preservation methods, severe primary graft failure occurs in 10-20% of CLT recipients. (24) Its associated severe hypoxia, pulmonary hypertension, and lung edema complicate postoperative management. Although only two lobes are transplanted, LDLLT seems to be associated with less frequent primary graft failure. We believe that using a "small but perfect graft" is a great advantage in LDLLT.

Experienced centers have recently reported the incidence of bronchial complications in CLT to be about 5%. (25) Contraindications to CLT include current high-dose systemic corticosteroid therapy because it may increase airway complications, although low-dose pre-transplantation corticosteroid therapy (≤ 20 mg/day prednisone) is acceptable. (26, 27) We have accepted high-dose systemic corticosteroid therapy, as high as 50 mg/day of prednisone, in LDLLT. (7) Among 84 anastomoses, excellent bronchial healing was observed in 83 anastomoses. Various factors, such as short donor bronchial length, high blood flow in the small grafts implanted, well preserved lung parenchyma with short ischemic time, may contribute to better oxygen supply to the donor bronchus, resulting in excellent bronchial healing in LDLLT.

Bronchiolitis obliterans syndrome (BOS) has been the major obstacle after CLT. The USC group suggested that LDLLT was associated with a lower incidence of BOS especially in pediatric patients. (4) They also indicated that shorter ischemic time in LDLLT could explain the reduced incidence of BOS. In our 38 LDLLT recipients who survived longer than 6 months, eight recipients (21%) developed BOS. Interestingly, seven of the 8 recipients developed unilateral BOS and their FEV1 decline stopped within 9 months. Transplanting two lobes

obtained from two different donors appears to be beneficial in the long term because the contralateral unaffected lung may function as a reservoir in case of unilateral BOS.

9. ETHICAL CONSIDERATION AND FUTURE DIRECTIONS

The ethical concerns of LDLLT present an obvious dilemma. This procedure subjects two healthy donors to a right or left lower lobectomy that is associated with an expected risk of death between 0.5% to 1%, a complication rate of 10-20%, and the inevitable 15% reduction in pulmonary function. While there have been no deaths in the donor cohort, these disadvantages are to be carefully explained to the potential donors during the process of obtaining informed consent. It is very important to provide the donors a "cooling off" period. In our program, the interview is performed at least three times individually to provide potential donors multiple opportunities to question, reconsider, or withdraw as a donor.

Because of these ethical concerns, the most centers accept only very sick patients as LDLLT recipients. If CLT provides similar results, it is certainly a better option. The major obstacle is the shortage of suitable cadaveric donors, especially in some countries such as Japan. The use of LDLLT has decreased in USA, and the recent change by the Organ Procurement and Transplantation Network to an urgency/benefit allocation system for cadaveric donor lungs in patients 12 yr and older may further reduce the demand. Because LDLLT requires two healthy donors with a compatible blood type and larger lung than the recipient, such a method is not available for most candidates. Therefore, this operation would not be a sufficient solution for the donor shortage.

Even though most of our patients were very sick at the time of transplantation, our LDLLT result, a 5-year survival rate of 87.6%, is very encouraging. This result has suggested that LDLLT might provide a better outcome than CLT. The question remains whether LDLLT should be performed in less sick patients. Further experience in LDLLT will answer this question.

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