Living donor lobar grafts improve pediatric lung retransplantation survival

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Objective: Lung retransplantation is a controversial practice due to increased morbidity and mortality and the scarcity of available donor organs. Living donor lobar lung transplantation increases the number of available donor organs and facilitates a more organized procedure than traditional cadaveric donation for this complex reoperation. The purpose of this study was to evaluate our experience with pediatric lung retransplantation and to compare the outcomes of living donor lobar lung transplantation with cadaveric donation.

Methods: Retrospective review of a prospectively collected database identified 39 children who underwent lung retransplantation from 1991 to 2004. Retransplantation was performed with living donor lobar lung transplantation in 13 patients and cadaveric donation in 26 patients. Short- and long-term outcomes were compared between the 2 groups.

Results: Perioperative mortality was 1/13 (7.7%) in the patients who had living donor lobar lung transplantation versus 11/26 (42.3%) in the cadaveric donation group ($P = .03$). Five-year survival for living donor lobar lung transplantation and cadaveric donation was 40.4% and 29.7%, respectively ($P = .27$). Both groups had a significant improvement in their forced expiratory volume in 1 second 6 months after retransplantation ($P < .001$). Multivariate analysis identified the use of cadaveric donation (relative risk = 6.16, $P = .001$) and early graft dysfunction (relative risk = 6.19, $P = .001$) as the major independent predictors of decreased survival following retransplantation.

Conclusions: Living donor lobar lung transplantation reduces perioperative mortality and is an independent predictor of improved survival following pediatric lung retransplantation. This strategy offers significant benefit for this high-risk group and preserves the limited supply of donor lungs for other children at risk of dying while waiting for lung transplantation.

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Lung retransplantation has been used at our center for highly selected patients with bronchiolitis obliterans syndrome (BOS) and acute graft dysfunction. Acute graft dysfunction is the leading cause of perioperative mortality and accounts for over 40% of early deaths.¹ BOS develops in 45% of pediatric lung recipients within 5 years and is the most common cause of late graft failure and death.¹ The only treatment for many of these patients is retransplantation. It is a

Abbreviations and Acronyms

- BOS = bronchiolitis obliterans syndrome
- CD = cadaveric donor
- LDLT = living donor lobar lung transplantation

controversial practice because of higher morbidity and lower survival compared with primary transplantation.²⁻⁵ In addition, the donor lung shortage raises ethical questions about the use of the precious cadaveric lung resource for retransplantation while other children die waiting for their first lung transplant.

Living donor lobar lung transplantation (LDLT) was developed in 1993 in response to the mismatch between supply and demand for those individuals awaiting lung transplantation.⁶ As more patients are being listed for lung transplantation, the median waiting time for cadaveric organs has doubled and more patients die on the waiting list.⁷ Our center has used LDLT for retransplantation since 1994. It augments the donor pool for retransplantation and preserves the cadaveric donor pool. In addition, LDLT facilitates a more elective and organized operation and reduces the ischemic time in this high-risk group. The purpose of this study was to evaluate our experience with pediatric lung retransplantation at a single center and compare the outcomes using LDLT and traditional cadaveric donors (CDs).

Materials and Methods

Patients

From November 1991 through September 2004, 39 lung retransplantations were performed at St Louis Children’s Hospital, Washington University School of Medicine. Thirty-eight of the 39 initial lung transplantations were performed using CDs. Thirteen of the retransplantations were performed using LDLT and 26 with CDs.

The donor lobectomies for LDLT were performed by 2 separate operating teams at Barnes-Jewish Hospital and utilized the right and left lower lobes from 2 different donors. Our strategy for LDLT selection and operative technique were recently reviewed.⁸

Pretransplant Diagnosis

The characteristics of patients undergoing lung retransplantation are listed in Table 1. The oxygen requirements were similar in both groups ($P = .2$) with 20% to 40% of the patients requiring mechanical ventilation prior to retransplantation. The 2 indications for retransplantation were BOS (80%) and primary graft dysfunction (20%). BOS was the most common indication and the timing of retransplantation depended on the severity of the clinical picture and the judgment of the pulmonary transplant team. These patients were highly motivated, adherent to their treatment protocols, and had good social support systems. Primary graft dysfunction was treated with standard ventilatory support, intensive hemodynamic support, and nitric oxide when the pulmonary artery pressures or pulmonary vascular resistance were elevated. Only those patients demonstrating a progressive deterioration were considered for retransplantation. In addition, these patients had to be free of sepsis and without any evidence of other organ failure.

Transplantation Technique

All retransplantation procedures were performed using cardiopulmonary bypass and 38 of 39 were bilateral. Only 1 unilateral retransplantation was performed using a CD for a patient with acute graft failure. During the 13-year series, there was no difference in the distribution of LDLT and CD retransplantation. Bilateral anterolateral transsternal (clamshell) thoracotomies were performed for the 38 sequential lung retransplantations, and bronchial anastomoses were wrapped with donor and recipient peribronchial tissue. The bronchial anastomosis was performed using monofilament absorbable sutures in a running fashion for the membranous portion and in an interrupted fashion for the cartilaginous portion. A Broviac catheter (Bard Systems Inc, Salt Lake City, Utah) was placed to maintain chronic vascular access. Vascular anastomoses

TABLE 1. Baseline characteristics

	LDLT (n = 13)	CD (n = 26)	P value
Age (y)	17.3 ± 3.3	13.2 ± 5.6	.020
Gender (female)	7 (53.8%)	11 (42.6%)	.520
Primary diagnosis			
Cystic fibrosis	11 (84.6%)	13 (50.0%)	.056
Pulmonary vascular disease	2 (15.4%)	5 (19.2%)	
Other pulmonary disease	0	8 (30.8%)	
Indication for retransplantation			.694
Bronchiolitis obliterans	11 (84.6%)	20 (76.9%)	
Primary graft failure	2 (15.4%)	6 (23.1%)	
Oxygen requirement			.204
None	0	3 (11.5%)	
O ₂ support	10 (76.9%)	13 (50.0%)	
Ventilated	3 (23.1%)	10 (38.5%)	
Time from first transplant (d)	1046 ± 849 944 (IQR: 341-1685)	1318 ± 1256 747 (IQR: 251-2409)	.800

IQR, Intraquartile range.

TABLE 2. Perioperative and surgical morbidity

	LDLT (n = 13)	CD (n = 26)	P value
Type of transplant performed			
Bilateral	0	25 (96.2%)	
Single	0	1 (3.8%)	
Bilateral lobar (living)	13 (100%)	0	
Ischemic time (minutes)			
First lung	88.6 ± 23.1	274.8 ± 63.1	<.001
Second lung	102.3 ± 28.0	324.1 ± 70.6	<.001
Cardiopulmonary bypass time (minutes)	250.2 ± 49.7	191.3 ± 45.6	.001
Required reexploration	6 (46.2%)	12 (46.2%)	.999
Required ECMO support posttransplant	1 (7.7%)	4 (15.4%)	.648
Early graft dysfunction	5 (38.5%)	13 (50.0%)	.734
Acute renal failure	2 (15.4%)	9 (34.6%)	.276
Required reintubation	6 (46.2%)	16 (61.5%)	.497
Length of mechanical ventilation (days)	6 (IQR: 4-13)	8 (IQR: 3-27)	.520
Length of stay in ICU (days)	8 (IQR: 7-15)	10 (IQR: 5-29)	.643
Length of stay in hospital (days)	29 (IQR: 14-32)	18 (IQR: 13-49)	.881
Hospital mortality	1 (7.7%)	11 (42.3%)	.034

ECMO, Extracorporeal membrane oxygenation; ICU, intensive care unit; IQR, intraquartile ranges.

were performed with running nonabsorbable suture. After the first graft is implanted, we have the perfusionist leave blood in the heart from the cardiopulmonary bypass circuit so that there is ejection into the pulmonary vasculature to a pulmonary artery pressure of around 20 mm Hg systolic. The lung is ventilated at pressures of 20/5 cm H₂O until the second bronchus is opened and then ventilation is discontinued.

Immunosuppression and Surveillance

All patients were treated with triple immunosuppressive therapy consisting of cyclosporine or tacrolimus, azathioprine or mycophenolate mofetil, and prednisone. Patients received standardized prophylaxis against *Candida* species, *Pneumocystis carinii*, and, for patients at risk, cytomegalovirus. All patients were followed up continuously at our center. Surveillance bronchoscopy with transbronchial biopsies were performed at regular intervals to rule out acute rejection. Biopsies were unilateral in cadaveric donors and bilateral in living lobar donors because the lower lobes came from 2 different donors. Acute rejection was graded according to the classification of the International Society for Heart and Lung Transplantation.⁹ Acute rejection was treated with bolus doses of methylprednisolone (10 mg/kg) daily for 3 days. Refractory acute rejection was treated with a 10-day course of antithymocyte globulin followed by a change in maintenance immunosuppression. Pulmonary function tests were also performed at regular intervals. Children under the age of 5 years who were unable to cooperate for standard pulmonary function tests were evaluated with infant pulmo-

TABLE 3. Late morbidity

	LDLT (n = 13)	CD (n = 26)	P value
Treated for airway complication	1 (7.7%)	3 (11.5%)	.999
Vocal cord paralysis	1 (7.7%)	1 (3.8%)	.999
Chronic renal insufficiency	6 (46.2%)	9 (34.6%)	.508
Diaphragm dysfunction	4 (30.8%)	8 (30.8%)	.999
Diagnosed with PTLT	1 (7.7%)	1 (3.8%)	.999
Acute rejection episodes	1.4 ± 2.0	0.9 ± 1.5	.347
No. of biopsies performed	7.6 ± 5.7	6.9 ± 5.2	.404

PTLT, Posttransplant lymphoproliferative disorder.

nary function tests.¹⁰ The majority of patients received a portable handheld spirometer to measure pulmonary function on a daily basis at home. BOS was defined according to standard spirometric criteria or by lung biopsy.¹⁰

Statistical Analysis

Normally distributed continuous data are expressed as mean ± standard deviation. Medians with intraquartile ranges are used when continuous data is skewed. Categorical data are expressed as counts and proportions. Comparisons were performed with paired and independent, 2-tailed *t* tests for means of normally distributed continuous variables, and the Wilcoxon rank-sum test for skewed data. Chi-square or Fisher exact test were used to analyze differences in proportions among the categorical data. Kaplan-Meier estimate was used to estimate survival and freedom from BOS. Survival and BOS-free survival comparison between groups of patients was completed using the Mantel-Haenszel log-rank test. Cox multivariate proportional hazards regression model was used to identify independent risk factors for death in the studied patient population including the variables of age, time from primary transplantation to retransplantation, type of allograft utilized, need for mechanical ventilation at the time of retransplantation, primary end-stage lung disease, indication for retransplantation, mean allograft ischemic time, and the occurrence of early graft dysfunction. All data analysis was performed using SPSS (SPSS 11.0 for Windows: SPSS Inc, Chicago, Ill). The Washington University Medical Center Human Studies Committee granted approval for this research.

Results

Perioperative

The length of cardiopulmonary bypass and the ischemic times are listed in Table 2. The ischemic times were dramatically shorter in the LDLT group. Post-retransplantation hospitalization variables including days mechanically ventilated, length of stay in the intensive care unit, and hospital length of stay were compared between the 2 groups. There were no significant differences in these post-retransplantation variables (*P* > .52).

Surgical Morbidity

Surgical morbidity was relatively high in both groups but not statistically different (Table 2). We have defined early

Figure 1. Freedom from BOS. Kaplan-Meier analysis comparing freedom from BOS between LDLT and CD lung retransplantation.

graft dysfunction as requiring mechanical ventilation for more than 7 days or a chest radiograph with a characteristic diffuse bilateral infiltrate.

Late Outcomes

Late outcomes are reported in Table 3 and were not significantly different between the groups. Acute rejection is reported as the number of episodes per patient along with the number of biopsies performed.

Freedom from BOS at 5 years was 90% for LDLT and 47.2% for CD ($P = .41$; Figure 1). Although the LDLT group had half the incidence of BOS at 5 years, the 2 groups were not significantly different due to the small sample size and possible type II error. Pulmonary function was compared between the two groups for those patients who survived 6 months (Figure 2). Both groups had a significant improvement in their forced expiratory volume in 1 second 6 months after retransplantation ($P < .001$) but the degree

Figure 2. Pulmonary function testing. Improvement in percent predicted forced expiratory volume in 1 second 6 months after retransplantation.

Figure 3. Survival following pediatric lung retransplantation. Kaplan-Meier analysis of survival comparing LDLT with CD lung retransplantation.

of improvement was higher in the CD group receiving bilateral complete lung transplants.

Mortality

The hospital mortality was 7.7% (1/13) for LDLT and 42.3% (11/26) for CD ($P = .03$). The 1 death in the LDLT group was secondary to infection in a 14-year-old boy who was initially transplanted for cystic fibrosis. He was the only 1 of 3 ventilated patients in the LDLT group to die perioperatively. The causes of death for the CD group were graft failure/respiratory failure ($n = 6$), infection ($n = 4$), and multisystem organ failure ($n = 1$). Four of 10 patients who were mechanically ventilated prior to retransplantation in the CD group had perioperative deaths. The Kaplan-Meier 5-year survival was 40.4% for LDLT and 29.7% for CD ($P = .27$; Figure 3).

TABLE 4. Results of multivariate analysis of prognostic factors influencing survival for patients following retransplantation

Variable	n	Relative risk	95% confidence interval	P value
Type of allograft utilized				
Living lobar	13	1.000	—	—
Cadaveric	26	6.162	2.050-18.519	.001
Early graft dysfunction				
No	21	1.000	—	—
Yes	18	6.192	2.143-17.888	.001
Age at transplantation (y)	39	1.295	1.123-1.492	<.001
Time to retransplantation (y)	39	0.702	0.559-0.881	.001

Requiring mechanical ventilation at the time of retransplantation, primary end-stage lung disease diagnosis, indication for retransplantation, and mean allograft ischemic time were covariates entered into the model but were not found to be significant predictors.

Prognostic Factors Influencing Survival

A Cox proportional hazards model was used to identify independent prognostic factors influencing survival (Table 4). The two major predictors of decreased survival were use of cadaveric donors and the presence of early graft dysfunction. A shorter time to retransplantation and older age of the recipient were minor prognostic factors.

Functional Status

Current follow-up data on 13 surviving patients were obtained from clinic records. Ten children are fully active and able to participate with school and normal activities of daily living. Three children are limited in their activities due to complications resulting from chronic renal insufficiency. They have required dialysis and are being evaluated for possible renal transplantation.

Discussion

Lung retransplantation poses an ethical dilemma between maximizing the distribution of the scarce donor lung supply to the greatest number of patients versus optimizing the outcome of individual patients. It is even more difficult when the patients are children and the mortality on the waiting list approaches 30%. The literature provides little data on pediatric lung retransplantation because the majority of reports deal exclusively with adults.^{3,11} This provided the incentive for our group to investigate the use of LDLT in retransplantation.

LDLT dramatically reduced ischemic time (Table 2) because there was no extended travel time associated with procurement from distant centers. In addition, the donor lobectomies were carefully coordinated with the recipient retransplantation, facilitating a more elective and organized operation. One may anticipate that the dramatic reduction in ischemic time due to LDLT would decrease the incidence of early graft dysfunction but this was not observed in our series (Table 2). One explanation for this is due to our liberal definition of early graft failure, which includes mechanical ventilation for 7 days or diffuse bilateral infiltrates. However, no patients in the LDLT group died from early graft dysfunction, which was the most common cause of hospital mortality in the CD group (6/11 deaths). Only 1 patient in the LDLT retransplantation group died perioperatively, secondary to infection. Our 8% perioperative mortality with LDLT retransplantation compares favorably to the 12% perioperative mortality following primary LDLT transplantation reported by Starnes and colleagues.¹² This is contrasted by the 42% hospital mortality in the CD retransplantation group. More than one third of these patients required mechanical ventilation prior to retransplantation and 50% suffered early graft dysfunction. The increased perioperative mortality in the CD retransplantation group is similar to recent reports and reflects the complexity of the procedure

and the poor preoperative functional status of these children.^{3-5,11}

The 5-year survival for the LDLT and CD groups was 40.4% and 29.7%, respectively ($P = .27$; Figure 3). The improvement in survival for the LDLT group was not statistically significant because the sample sizes were small and there may be a type II error (the chance you can miss an effect even though one exists). The smaller the sample, the more likely you are to commit a type II error, because the confidence interval is wider and is therefore more likely to overlap zero. However, our 5-year survival of 40% for the LDLT retransplants is similar to the 45% 5-year survival of primary LDLT reported by Starnes and colleagues.¹² Importantly, their group has published that intubated patients (odds ratio = 3) and patients undergoing retransplantation are at significantly high risk because of poorer outcomes. Although one would anticipate that patients requiring mechanical ventilation prior to retransplantation would be at higher risk, univariate and multivariate analysis of this series did not demonstrate mechanical ventilation to be an independent predictor of mortality.

The data presented in this series demonstrates that LDLT offers advantages over cadaveric donation and may be the preferred method of retransplantation for this high-risk group. In addition, multivariate analysis demonstrated that LDLT reduced the risk of death following retransplantation by a factor of 6 (Table 4). BOS is an important determinant of survival and quality of life following lung transplantation. Unfortunately, children may be more susceptible to BOS with incidence rates from 45% to 75% within 5 years.^{1,13} LDLT has been reported to reduce the incidence of BOS in pediatric patients.^{14,15} The 5-year freedom from BOS following LDLT retransplantation in this series was 90% with infection being the most common cause of late death. The incidence of BOS between LDLT and CD was not statistically significant but the differences may become significant with longer follow-up (Figure 1). One may speculate that the increased severity of reperfusion injury in the CD group influenced the trend of developing BOS. As stated previously, early graft dysfunction was not the cause of mortality for any patient in the LDLT group but resulted in the death of 6/11 patients in the CD group. Pulmonary function improved dramatically in both groups (Figure 2). In contrast to previous reports, our data demonstrated a larger improvement for the CD group receiving complete bilateral lung transplants.¹⁵ Importantly, the functional status of patients surviving retransplantation was excellent: 77% were fully active and 23% were partially limited.

LDLT is an enormous undertaking with physical and psychological repercussions. It requires a dedicated staff of lung transplant coordinators, social workers, pulmonologists, thoracic surgeons, and a large commitment from the hospital. On average, 5 individuals are screened as potential

lobar donors to come up with the 2 that will be satisfactory. A well-trained team of transplant coordinators and social workers are crucial to facilitate the screening process, help with travel plans and housing, and coordinate reimbursement issues. Our criteria for living lobar lung donation were reviewed previously.⁸ Every effort is made to keep the evaluation team separate from the transplanting team for ethical purposes. An extensive discussion describing the donor lobectomy procedure, the potential operative risks to the donor, and the uncertain outcome for the recipient was conducted with each potential donor. The entire evaluation was completely closed to other family members and physicians and if a patient wanted to withdraw, the reason remained anonymous. Although we have experienced no donor mortality with 62 donor lobectomies, more than half of donors had postoperative complications and this needs to be factored into the decision when LDLT is being considered.⁸

In conclusion, lung retransplantation in children can be performed successfully but has increased morbidity and mortality over primary transplantation. Selecting patients for retransplantation is an extremely difficult process when so much has been invested by the patient, their family, and the transplant team. Patient selection needs to remain strict because of the increased risk involved and the scarcity of donor lungs. This series demonstrates that LDLT may be the procedure of choice for retransplantation. It facilitates an organized operation, dramatically reduces ischemic time and hospital mortality, and preserves the pool of cadaveric donor lungs for other patients on the waiting list. LDLT is an independent predictor of improved survival following retransplantation and with longer follow up it may demonstrate a reduction in BOS and improved 5-year survival.

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