Redo lung transplantation for acute and chronic lung allograft failure: long-term follow-up in a single center

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Abstract

Objective: This study was undertaken to evaluate outcomes of redo lung transplantation (LT) for acute and chronic graft failure. Methods: Between 1988 and 2007, 388 LT procedures were performed on 369 patients. From those, 17 (4.6%) patients had redo LT once and 2 patients had redo LT twice. Patient survival and recurrence of bronchiolitis obliterans syndrome (BOS) after redo LT were reviewed. Results: The overall survival rates of the 17 redo LT recipients at 1, 2 and 5 years were 59 ± 23%, 59 ± 23% and 42 ± 25%, respectively. For the chronic graft failure group (n = 12), survival rates at 1, 2 and 5 years were 67 ± 26%, 67 ± 26% and 44 ± 30%, respectively. These survival rates were significantly lower than the survival rates observed in our experience after primary LT (n = 352, 1-, 2- and 5-year survival rates of 88 ± 4%, 80 ± 4% and 65 ± 5%, respectively). For the acute graft failure group (n = 5), the 1-year survival rate was 40%; two patients remain free from BOS. Two patients had a second redo LT, one died from multi-organ failure on postoperative day 86 and the other died from pulmonary aspergillosis on postoperative day 214. Conclusions: Redo LT is a valid therapeutic option for selected patients with BOS and might be an option for highly selected patients with acute lung graft failure. Outcomes from a second redo LT are poor, and a second lung retransplantation must be used very cautiously, if at all.

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Keywords: Rejection; Reoperation; Transplantation; Retransplantation; Lung

1. Introduction

Survival rates in lung transplantation (LT) recipients have progressively improved, and LT has become an established therapy for a variety of end-stage pulmonary diseases since the first human LT was performed by Hardy and colleagues in 1963 [1]. The improvement in post-transplant survival rates is largely due to careful patient selection, improved surgical techniques, better immunosuppressive regimens, and more aggressive antibiotic prophylaxis and treatment of infectious complications. The 23rd official report by the registry of the International Society for Heart and Lung Transplantation (ISHLT) shows the 1-year survival rate after primary LT increased from 70% in the era 1988 through 1994 to 81% in the era 2000 through 2004, an improvement of 11% and a relative improvement of 15% [2]. However, beyond the first year, the downward slope in survival in the three eras was nearly parallel, suggesting that management strategies have been more effective in reducing early fatal complications than in moderating later, potentially lethal problems. In addition, bronchiolitis obliterans syndrome (BOS) remains the primary cause of death beyond the first year after transplant with an incidence of approximately 30% [2].

Primary graft dysfunction (PGD), severe airway complications, refractory acute rejection, and progressive BOS can lead to irreversible allograft dysfunction and respiratory failure following primary LT. Although various treatment protocols for BOS have been attempted [3,4], these strategies have not generally provided satisfactory results for recipients with progressive, high-grade BOS. Retransplantation can be performed to treat severe post-transplant allograft complications if refractory to all other interventions, and redo LT may provide the only therapeutic option for recipients of primary LT when refractory graft failure occurs. However, outcomes following retransplantation have
been perceived as significantly worse than outcomes following primary LT. Because of ethical concerns about proper organ distribution when an overall organ scarcity prevents successful transplant of many waitlisted candidates and various reports of poor outcome following retransplantation have been published, the value of retransplantation has been open to question.

Lung retransplantation is clearly a higher risk procedure than a first-time transplant. According to the Organ Procurement and Transplantation Network (OPTN) report for the 1997–2004 time period, the 1-year survival rate in the redo LT group was 59% and the 5-year survival was 36% (http://www.optn.org/latestdata). More recent data, however, suggest that survival following retransplantation for certain recipient groups approach that for primary LT, and outcomes following lung retransplantation have generally improved [5–7]. Aigner and colleagues [5] analyzed results for a cohort of 46 patients and reported that retransplantation for PGD had the worst outcomes, whereas retransplantation for BOS appears to provide survival rates that are similar to long-term survival rates for primary LT, and retransplants for airway complications also had relatively good outcomes. A recent report from the Hannover Lung Transplant group [6] represents the largest single-center series (n = 54), and the authors have clearly identified a group of patients for whom redo LT has an equivalent outcome to a first-time transplant, with an impressive 5-year survival rate of 62% in patients undergoing redo LT for BOS. A recent analysis of OPTN data by Kawut and colleagues [7] supports these single-center observations and showed progressively improving outcomes following retransplantation when older vs more recent (‘modern’) cohorts were analyzed, although poor outcome was observed for patients retransplanted within 30 days of their initial primary transplant.

From an ethical standpoint the ultimate role and potential benefit of redo LT in an era marked by a scarce and static donor organ supply that meets the needs of only one fourth of listed candidates needs to be clarified [8,9]. Because of wide differences in reported survival for various recipient indications and the ongoing shortage of donor lungs, redo LT remains a controversial procedure. The purpose of our study was to evaluate outcomes of redo LT after acute and chronic graft failure in our institution since 1988, to help determine whether redo LT is a valid therapeutic option for patients with primary graft failure.

2. Patients and methods

We performed a total of 388 LT procedures in 369 patients in our institution between 1988 and 2007. Seventeen (4.6%) of these recipients underwent redo LT procedures. Fifteen (4.1%) patients who had redo LT once, and two patients (0.5%) underwent a second redo LT twice when their retransplanted allograft failed. There were six men and 11 women, and the mean age was 48 ± 10 years (range 31–63 years). These 17 patients will be the focus of this study. The main indication for primary LT was chronic obstructive pulmonary disease (COPD) in five, idiopathic pulmonary fibrosis (IPF) in six, emphysema associated with α1-antitrypsin deficiency in two, cystic fibrosis (CF) in two, and primary pulmonary hypertension (PPH) in two patients. Patient demographics are summarized in Table 1. Indications for redo LT were chronic graft failure secondary to BOS in 12 patients (71%), early primary graft failure in four (24%) and severe dehiscence of the bronchial anastomosis in one patient (5.9%). All patients were oxygen dependent, and eight of them (47%) required mechanical ventilator support at the time of retransplantation. In addition, three of eight ventilated patients received

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient demographics</th>
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<tr>
<td><strong>Chronic graft failure group</strong></td>
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<tr>
<td>1</td>
<td>M 31 IPF 760 — BOS — BLT BLT —</td>
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<tr>
<td>2</td>
<td>F 57 COPD 762 — BOS — Lt. SLT Rt. SLT —</td>
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<td>3</td>
<td>M 39 IPF 1534 — BOS — Lt. SLT Rt. SLT —</td>
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<td>4</td>
<td>M 36 IPF 269 3121 BOS — BLT Rt. SLT Rt. SLT —</td>
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<td>5</td>
<td>M 32 CF 626 — BOS Vent BLT BLT —</td>
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<td>6</td>
<td>F 39 COPD 1541 — BOS — BLT BLT —</td>
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<td>7</td>
<td>F 40 CF 220 — BOS Vent BLT BLT —</td>
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<td>8</td>
<td>F 40 PPH 653 — BOS — BLT Rt. SLT —</td>
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<td>9</td>
<td>F 53 ATD 4978 — BOS Vent Rt. SLT Lt. SLT —</td>
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<td>10</td>
<td>F 55 COPD 3438 — BOS — Rt. SLT Lt. SLT —</td>
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<tr>
<td>11</td>
<td>F 55 PPH 191 — BOS — BLT Lt. SLT —</td>
</tr>
<tr>
<td>12</td>
<td>F 57 IPF 203 — BOS Vent BLT Rt. SLT —</td>
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| **Acute graft failure group** |  |
| 13 | F 52 COPD 8 91 Acute rejection ECMO Lt. SLT Lt. SLT Rt. SLT — |
| 14 | F 56 IPF 4 — PGD ECMO Lt. SLT BLT — |
| 15 | F 63 COPD 5 — PGD ECMO Lt. SLT Lt. SLT — |
| 16 | M 46 ATD 22 — Bronchial dehiscence — BLT Rt. SLT — |
| 17 | M 59 IPF 20 — Acute rejection Vent Rt. SLT Rt. SLT — |

support with an extracorporeal membrane oxygenator (ECMO) just prior to redo LT. The median time between primary LT and redo LT was 269 days (range, 4—4978 days). The redo LT procedure was single LT in 14 cases and bilateral LT in 5 cases. Patients who had a single redo LT underwent three different retransplantation operative techniques including ipsilateral single lung transplantation (SLT) after a primary SLT (n = 3), contralateral SLT after primary SLT (n = 6) and SLT after primary double LT in five patients. Hence, an old graft was left in situ in 10 redo LT recipients (59%). Patient survival and BOS recurrence were reviewed. Patient survival length was calculated from the second LT procedure. BOS was defined according to the criteria of the ISHLT definition [10].

2.1. Data acquisition and follow-up

The institutional review board committee of our institution approved this study. Data were collected prospectively and analyzed retrospectively. The lung transplant database was reviewed for demographic, operative, perioperative, and outcome data. Follow-up was obtained through telephone interviews, and outpatient chart review. The longest follow-up was 3360 days (mean 1203 ± 1159 days for chronic and 436 ± 518 days for the acute group). Follow-up was 100% complete.

2.2. Statistical analysis

Categorical data were summarized with frequency distributions and percentages. Values of continuous variables were expressed as means ± standard deviations. The Kaplan—Meier survival method was used to assess both primary and redo LT patient survival. Log-rank tests were used to assess statistical significance in survival differences between the groups. Variables tested include: redo versus primary excluding redo LT cases, and ventilator dependence. To test for differences in survival curves up to a given time point, say 1 year, survival was censored at the point of interest. A p value less than 0.05 (two-sided) was considered to be statistically significant. All analyses were performed using the SAS statistical software program (Version 9.1 for Windows; SAS Institute, Cary, NC).

3. Results

The overall survival rate of the 17 redo LT recipients at 1, 2 and 5 years were 59 ± 23%, 59 ± 23% and 42 ± 25%, respectively (Fig. 1). For the chronic graft failure group, actual survival rates at 1, 2 and 5 years were 67 ± 26%, 67 ± 26% and 44 ± 30%, respectively. These survival rates were significantly lower than the survival rates observed in our experience after primary LT (n = 352, excluding 17 redo LT recipients, 1-, 2- and 5-year survival rates of 88 ± 4%, 80 ± 4% and 65 ± 5%, respectively; log-rank test, p = 0.023: Fig. 1). For the acute graft failure group, however, the 1-year survival rate was 40%.

The causes of death are detailed in Table 2. Eleven patients died during follow-up (two early deaths within the first 30 days after redo LT). Infection was the cause of death in five of these cases (45% of all deaths). The primary retained graft was the initial site of the fatal infection in two of these five patients who died from infection (40%). In patient 2, recurrent pulmonary aspergillosis occurred in the retained graft, and this infection was ultimately the cause of disseminated aspergillosis at day 918 after redo LT. In patient 15, sepsis from pneumonia in the retained graft due to Pseudomonas aeruginosa developed at day 46 after redo LT. Two of them (patient 5 and 8) died from pneumonia in the second graft due to P. aeruginosa and Escherichia coli, respectively. Identification of the pathogenic bacteria was obtained by a protected specimen brush during fiberoptic bronchoscopy. Two of all redo LT recipients (patient 4 and 13) had the third LT at day 3121 and 91 after the second LT because of recurrence of BOS stage 3, respectively. Patient 4 died from multi-organ failure due to cecal rupture after 86 days of the third LT. In patient 13, pulmonary aspergillosis in the third graft developed at day 214 after the third LT.

The overall rates of freedom from BOS (stage 1, 2, or 3, ISHLT classification) at 1, 2 and 5 years were 84 ± 20%, 72 ± 22% and 48 ± 43%, respectively (Fig. 2). For the chronic graft failure group, the rates of freedom from BOS were 90 ± 19%, 75 ± 21% and 50 ± 45%, respectively. For the acute graft failure group, 1-year freedom from BOS was 67%. At last follow-up, four redo LT recipients had BOS recurrence, two of whom died from BOS, and the two others underwent the third LT.

The survival rates in redo LT recipients with and without ventilator dependence and/or ECMO support before redo procedure are shown in Fig. 3. The actual survival rate at 1 year in the ventilator and/or ECMO dependent group (n = 8) tended to be lower than that in the non-dependent group (n = 9). However, there was no significant difference (p = 0.09).

The presence of a retained graft was not a risk factor for the survival in redo LT recipients (Fig. 4).

4. Discussion

We evaluated the outcomes after redo LT for acute and chronic (BOS) graft failures at our transplant center and report the data as a single-center experience. All LT
procedures included in this study were performed over a period of nearly 20 years, and all redo transplant procedures were performed within the past 15 years. According to the OPTN report between 1997 and 2004, the overall survival rates in the redo LT group at 1 and 5 years were 59% and 36%, respectively (http://www.optn.org/latestdata). The overall survival rates for 17 redo LTs performed at our institution were 59% at 1 year and 42% at 5 years. The 5-year survival for recipients at our institution was higher than that recorded in the OPTN report, although the 1-year survival was identical to OPTN data. However, the survival rate in the chronic graft failure (BOS) group was somewhat lower, compared with recent results from other single-center reports [6,11,12]. The reason for this discrepancy in survival might be an institutional bias that includes the timing and indication for redo LT and patient comorbidity as well as surgical and medical management strategies.

Novick and Stitt [13] analyzed many aspects of redo LT a decade ago in the multi-center report on 230 retransplant procedures performed at 47 centers across the United States, Canada, Europe, and Australia. A multivariate analysis of this multi-center database identified significant predictors of improved survival as ambulatory status or lack of ventilator support preoperatively and redo LT after 1991 (‘era effect’). The Hannover Lung Transplant group reported that patients on mechanical ventilation before a redo LT procedure showed a 1-year survival of only 50% as compared to 80% for ambulatory patients [6]. The Vienna group reported 1- and 5-year survival as 52% and 29% for PGD versus 89% and 61% for BOS [5]. Similarly, 1-year survival following retransplantation for PGD was 50% in the Hannover cohort, but 1- and 5-year survival for BOS was 78% and 62%. These reports of improved outcome with redo LT at single centers are complemented by the analysis of OPTN data that demonstrate a significant improvement in survival for patients retransplanted from 2001 to 2006 versus those retransplanted from 1990 to 2000 [7]. Although the number of patients was small in our cohort, the 1-year survival in patients who had ventilator and/or ECMO support prior to retransplant was below 50%. The Hannover and Vienna reports [5,6], in addition to our own

![Freedom from bronchiolitis obliterans syndrome (stage 1, 2, or 3, ISHLT classification) following redo lung transplantation (LT).](image1)

![Actuarial survival rates following redo lung transplantation (LT) with and without ventilator dependence and/or extracorporeal membrane oxygenator (ECMO) support before redo procedure.](image2)
Iacono and colleagues [14] indicated that the topical delivery of cyclosporine significantly improved the survival and freedom from BOS after redo LT. To reduce the recurrence of BOS after transplant, immunosuppressive or other non-surgical therapies for recipients with progressive BOS. The rate of freedom from BOS after redo LT is approximately 50% at 5 years according to several previous reports [6,11,12]. In our series freedom from BOS is similar (48% at 5 years). These results indicate that the incidence, morbidity, and mortality of BOS, new strategies to prevent and treat this condition, are still high.

Chronic graft rejection (BOS) remains a major cause of late death for primary LT as well as redo LT recipients. The recent ISHLT report shows that BOS accounts for approximately 30% of late deaths after primary LT, and 45% of LT recipients developed BOS within 5 years following primary LT [2]. Although various treatment protocols for BOS have been attempted [3,4], there is no apparent consensus concerning immunosuppressive or other non-surgical therapies for recipients with progressive BOS. The rate of freedom from BOS after redo LT is approximately 50% at 5 years according to several previous reports [6,11,12]. In our series freedom from BOS is similar (48% at 5 years). These results indicate that the incidence of BOS is not increased in redo LT, but BOS still remains a concern for both primary and redo LT procedures. The recent randomized trial for LT recipients reported by Iacono and colleagues [14] indicated that the topical delivery of cyclosporine significantly improved the survival and decreased the recurrence of BOS after transplant. To reduce the incidence, morbidity, and mortality of BOS, new approaches to treatment and prevention are much needed.

The optimal redo LT procedure still remains controversial. Brugiere and colleagues [11] reviewed 15 contralateral redo single LT recipients for BOS between 1988 and 2002, and evaluated the effect of the retained graft on outcomes. In their small series infection of the retained graft was a common cause of death and they suggested that the removal of the old graft was favorable whenever possible. Kawut and colleagues [7] recently reviewed a large series of 205 redo LT recipients from OPTN data pertaining to transplants performed between 2001 and 2006 and analyzed these data to detect predictors of mortality risk. According to their analysis, the type of redo LT procedure (initial: redo, double:double, double:single, single:double, and single:single [ipsilateral or contralateral]) did not seem to be related to outcomes. In addition, the authors compared the ‘modern’ redo LT recipients with the ‘historical’ redo LT recipients operated on between 1990 and 2000 (n = 184). They showed that despite an increase in recipients with retained grafts (double to single, and single to contralateral single) from 32% in the ‘historical’ cohort to 46% in the ‘modern’ cohort, the survival rate was significantly improved in the modern era. They suggested that the choice of redo LT procedure was not associated with outcome. Similarly, the presence of a retained graft from the initial transplant was not identified as a risk factor for survival in redo LT recipients in our patients (Fig. 4).

The redo LT procedure represents a major challenge in patients with acute graft failure due to complications such as acute PGD and airway dehiscence. Clearly, this is a very high-risk patient population, and it is difficult for a single center to accumulate a large number of recipients who undergo redo LT for refractory PGD. Nonetheless, several investigators have reported a lower survival after redo LT for acute PGD, and the actuarial survival rate was 30–50% at 1 year [6,11,15]. In the present cohort, only five patients with PGD received a redo LT procedure. Two of them are alive, and the 1-year survival rate was 40%. To recover from acute graft failure, ECMO support may be used as a life-saving therapy, and the ISHLT Extracorporeal Life Support Organization Registry reported that hospital mortality was 58% [16]. In the present study, three patients with acute graft failure had ECMO support prior to a redo LT procedure, but only one patient had long-term survival. Currently available literature suggests that ECMO may be an appropriate intervention, for acute graft failure, but it is more likely to provide benefit if used early rather than late after the onset of this complication [16,17]. Even though redo LT procedures can be performed after ECMO support, recovery in these critical conditions is difficult at best and should be pursued with careful consideration of risks versus benefit.

Redo LT procedures for chronic airway problems have been reported to have good results in the adult population [5]. Acute graft failure secondary to airway dehiscence however, remains a very high-risk endeavor, as has been documented by the Hannover group [6]. For primary LT procedures, several techniques have been developed in an attempt to protect or perform the bronchial anastomosis. These techniques include keeping the donor bronchus as short as possible, wrapping the anastomosis with vascularized pedicles, and the use of end-to-end versus telescoped anastomotic techniques. However, there is no consensus on the ideal surgical technique for the bronchial anastomosis, and significant variation exists among LT centers [18,19]. One could speculate that for redo LT procedures, the frequent coexistence of infection and/or rejection at the time of the redo TX poses problematic conditions for the bronchial anastomosis that usually do not exist with primary LT. However, there is no evidence to date that acute airway complications are more prevalent after redo LT, and no special techniques for creating airway anastomoses or for recipient management have been reported for prevention of airway dehiscence and other anastomotic complications [5–7,11,13,15].

Redo LT recipients are theoretically at higher risk of infection due to the chronic immunosuppression they receive prior to redo LT. Although optimization of immunosuppressive strategies for redo LT recipients has been suggested by others [9], at our institution, the same immunosuppressive regimens used for primary LT recipients have been applied for the redo LT patients. Higher risk of infection complications has not been documented in our patient population.
Further clarification of the role of HLA antibodies and redo LT outcomes is much needed. According to the data from the ISHLT, mismatches at the HLA-A and -B loci are significant risk factors for post-transplant mortality in primary LT recipients [2]. Similarly, autoimmunity to collagen V is emerging as a very important risk factor for developing advanced BOS following primary lung transplantation [20]. For kidney retransplantation, recipients who are re-exposed to mismatched HLA class I antigens, appear to be at heightened risk of early graft loss [21]. Unfortunately, our cohort is not large enough to provide any meaningful on HLA matching and redo LT outcomes. The contributions of the presensitized state and humoral allergenic immune responses are just emerging in primary LT, and we speculate that these factors play a significant role in retransplantation outcomes. Future studies may indicate whether more intensive immunosuppression for these patients is warranted.

From an ethical standpoint, the ultimate role and potential benefit of redo LT in an era marked by a scarce and static donor organ supply that meets the needs of only one fourth of listed candidates become very controversial [8,9]. Traditional outcomes data showed that first time lung transplants had nearly double the 5-year survival of redo lung transplants. By using the utilitarian principle of helping those who would benefit the most, redo LT recipients were ranked below primary LT recipients as regards donor organ allocation. However, another line of thought, the egalitarian principle, holds that those in need should have an equal opportunity to receive the required scarce treatment [9]. Therefore, traditionally, first time LT recipients seem to have had a priority over first time LT recipients. The Hannover group [6] has disturbed the ethical status quo by refuting the utilitarian argument against retransplantation after clearly showing outstanding results in a selected group of redo LT recipients. The utilitarian and egalitarian principles merit consideration and ongoing discussion, but these antagonistic considerations remain unresolved for redo LT.

Two recent major trends appear to be adding to this ethical controversy: First, since the implementation of new lung allocation scoring (LAS) system in the United States in May 2005 [22], waiting times for redo LT are shorter, and the proportion of lung allografts being used for redo LT have increased by as much as 60% [7]. The LAS system was designed to reduce the wait list mortality as well as to take disease severity and the likelihood of a successful outcome after transplantation into account. The LAS system may, therefore, need to incorporate the medical and ethical issues specific to redo LT in the future. Second, outcomes for all lung transplant recipients have gradually improved [2]. Although overall survival for redo LT patients is still worse than for those receiving initial transplantation [7] with the exception of a few centers [6], outcomes are not dissimilar from certain diagnoses that are traditional indications for transplantation, such as pulmonary arterial hypertension, especially when performed for late-onset BOS. In addition, it has been well documented that skillful selection of patients and meticulous management may continue to improve the outcomes of redo LT. Considering the increased numbers of redo LT being performed, it is of paramount importance that the lung transplant community promptly address the issues of fairness and allocation as they pertain to redo LT.

In conclusion, recent advances in surgical techniques, immunosuppressive regimens, and antibiotic prophylaxis and treatment have enabled redo LT to become a valid therapeutic option for selected patients with chronic graft failure due to BOS. Recent single-center analyses and an analysis of OPTN data support redo LT as an option for graft failure, and retransplantation should be considered on a case-by-case basis for recipients of primary LT whose allografts have developed severe dysfunction that is refractory to non-surgical interventions. Although redo LT can be performed for refractory acute graft failure, it is associated with significantly poorer outcome and should only be considered as an option for highly selected patients. Our data for patients who underwent a first redo LT showed reasonable survival. However, survival following a second redo LT appears to be poor, and its use must be approached with great caution and perhaps discouraged.

References


