Does reperfusion injury still cause significant mortality after lung transplantation?

Gorav Ailawadi, MD, Christine L. Lau, MD, Philip W. Smith, MD, Brian R. Swenson, MD, MS, Sara A. Hennessy, MD, Courtney J. Kuhn, Lynn M. Fedoruk, MD, Benjamin D. Kozower, MD, Irving L. Kron, MD, and David R. Jones, MD

Objectives: Severe reperfusion injury after lung transplantation has mortality rates approaching 40%. The purpose of this investigation was to identify whether our improved 1-year survival after lung transplantation is related to a change in reperfusion injury.

Methods: We reported in March 2000 that early institution of extracorporeal membrane oxygenation can improve lung transplantation survival. The records of consecutive lung transplant recipients from 1990 to March 2000 (early era, n = 136) were compared with those of recipients from March 2000 to August 2006 (current era, n = 155). Reperfusion injury was defined by an oxygenation index of greater than 7 (where oxygenation index = [Percentage inspired oxygen] × [Mean airway pressure]/[Partial pressure of oxygen]). Risk factors for reperfusion injury, treatment of reperfusion injury, and 30-day mortality were compared between eras by using χ^2, Fisher's, or Student's *t* tests where appropriate.

Results: Although the incidence of reperfusion injury did not change between the eras, 30-day mortality after lung transplantation improved from 11.8% in the early era to 3.9% in the current era ($P = .003$). In patients without reperfusion injury, mortality was low in both eras. Patients with reperfusion injury had less severe reperfusion injury ($P = .01$) and less mortality in the current era (11.4% vs 38.2%, $P = .01$). Primary pulmonary hypertension was more common in the early era (10% [14/136] vs 3.2% [5/155], $P = .02$). Graft ischemic time increased from 223.3 ± 78.5 to 286.32 ± 88.3 minutes in the current era ($P = .0001$). The mortality of patients with reperfusion injury requiring extracorporeal membrane oxygenation improved in the current era (80.0% [8/10] vs 25.0% [3/12], $P = .01$).

Conclusion: Improved early survival after lung transplantation is due to less severe reperfusion injury, as well as improvements in survival with extracorporeal membrane oxygenation.

Lung transplantation (LTX) is the preferred treatment for a variety of patients with end-stage pulmonary diseases. Primary graft dysfunction (PGD), the most severe form of ischemia and reperfusion injury (RI), remains the most common cause of early mortality, accounting for nearly 30% of early deaths after LTX.[1] RI is characterized by severe hypoxemia, increased airway pressures, acute pulmonary edema, and frothy endobronchial secretions that occur within 24 to 48 hours after implantation. In its most severe form, RI is termed PGD. Despite improvements in lung preservation and surgical technique, RI continues to affect 20% to 35% of transplant recipients.[1,2] A variety of factors appear to play a role in the development of RI, including graft preservation techniques, graft ischemic time, and unsuspected donor lung pathology, including pulmonary contusion, pulmonary embolism, and aspiration.

Supportive therapies, including fluid management, diuretic use, and judicious ventilator management, can help to treat RI, which typically resolves in 48 to 72 hours. Pulmonary vasodilators, including nitric oxide (NO) and epoprostenol, have been used in more severe forms of RI. Patients with severe RI might require extracorporeal membrane oxygenation (ECMO) support.

Early survival after LTX at our institution has improved. Recent data from the 2006–2007 Scientific Registry of Transplant Recipients annual report indicates 30-day and 1-year survival at our institution is 98.2% and 92.3%, respectively.[3] Because RI is the most common cause of early death after LTX, we hypothesized that these improved current survival rates might be due to a change in RI.

MATERIALS AND METHODS

Patient Population

From January 1990 to August 2006, 291 patients underwent LTX at the University of Virginia. Data from patients undergoing LTX were extracted from our Lung Transplant Registry and were approved by the University of Virginia Institutional Review Board (no. 12006). In March 2000, we reported that a heightened awareness of RI with early institution of ECMO can improve survival.[4] In that report RI was defined as an oxygenation index (OI) of greater than 7 (where OI = [Fraction of inspired oxygen {F_{IO_2}}] ×

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Address for reprints: Christine L. Lau, MD, Department of Surgery, University of Virginia, PO Box 800679, Charlottesville, VA 22908-0679 (E-mail: cll2y@virginia.edu).
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Abbreviations and Acronyms

ATGAM = antithymocyte globulin
CMV = cytomegalovirus
COPD = chronic obstructive pulmonary disease
ECMO = extracorporeal membrane oxygenation
F_{IO_2} = fraction of inspired oxygen
ISHLT = International Society for Heart and Lung Transplantation
LTX = lung transplantation
NO = nitric oxide
OI = oxygenation index
OPO = organ procurement organization
P/F = Pa_{O_2}/F_{IO_2}
PGD = primary graft dysfunction
PPH = primary pulmonary hypertension
RI = reperfusion injury

[Mean airway pressure]/[Partial pressure of oxygen]). OI of greater than 10 is considered severe RI.

Therefore we compared lung transplant recipients before March 2000 (early era, n = 136) with recipients after March 2000 (current era, n = 155) to determine whether there has been a change in the incidence, course, or treatment of RI. Risk factors for RI, treatment of RI, and 30-day mortality were compared between the early and current eras.

Our LTX database maintains data on characteristics, including age, sex, ethnicity, body mass index, diagnosis, and cytomegalovirus (CMV) status; operative events, including single versus double LTX, use of cardiopulmonary bypass (CPB), and graft ischemic time; and postoperative variables, including OI and mortality. Our preferred approach for single LTX was through a standard posterolateral thoracotomy, and that for double LTX was through a clamshell incision. CPB was used selectively. In 1996, NO became available at our institution for patients refractory to conventional ventilator management. Before 1998, donor lung preservation was performed with either Euro–Collins or University of Wisconsin solution. By 2000, lungs were exclusively flushed antegrade and retrograde with Perfadex (Vitrolife, Denver, Colo). All patients had complete follow-up.

Perioperative Immunosuppression and Infection Prophylaxis

Transplant recipients are started on antibiotics before incision and continued on antibiotic therapy until bronchial cultures are negative. Recipients also received 2.5 mg/kg azathioprine and 1 g of methylprednisolone before organ implantation. Before 2002, patients underwent induction immunosuppression consisting of 750 mg of methylprednisolone and antithymocyte globulin (ATGAM; 7-day taper starting with 15 mg/kg). After 2002, induction immunosuppression switched from ATGAM to daclizumab (1 mg/kg). Maintenance immunosuppression consisted of cyclosporine or tacrolimus, azathioprine (2 mg/kg) or mycophenolate mofetil (2 g), and prednisone (20 mg). Patients received CMV prophylaxis during the study period with ganciclovir (3 mg/kg twice daily) or valganciclovir (Valcyte; 900 mg daily; Roche, Nutley, NJ) from day 7 through day 21. After completion of ganciclovir, CMV prophylaxis was maintained with acyclovir (800 mg 4 times daily). In the setting of donor CMV^+/recipient CMV^-, ganciclovir was continued until day 90, and CMV–intravenous immunoglobulin (Cytogam; Genesis Bio-Pharmaceuticals, Hackensack, NJ) was administered (150 mg/kg on day 4 and weeks 2, 4, 6, and 8 and then 100 mg/kg on weeks 12 and 16).

Definition of RI

There are many scoring systems to determine the severity of PGD or RI after LTX. The gold standard test to determine this is not readily apparent. The International Society for Heart and Lung Transplantation (ISHLT) has developed a grading system based on Pa_{O_2}/F_{IO_2} (P/F) ratio and infiltrates on chest x-ray films.[5] A P/F ratio of less than 300 with chest x-ray infiltrates is considered grade 2 PGD, whereas a P/F ratio of less than 200 is considered grade 3 PGD, the most severe form. Before 1998, our transplant database maintained OI to determine RI severity. OI as an indicator for severity of lung injury was developed by critical care physicians and has been used to stratify patients in the Acute Respiratory Distress Syndrome Network trials.[6] The raw data of F_{IO_2}, Pa_{O_2}, and mean airway pressure were not recorded for each patient in the early years of our transplant database. Therefore to compare the early era (before March 2000) with the current era, OI was used in this study to document the severity of RI. As in our previous report, RI was defined as an OI of greater than 7.

Statistical Analysis

Statistical comparisons between groups were performed with the Student's t test for continuous variables. χ^2 Analysis and the Fisher's exact test were used, where appropriate, to compare categorical variables. Univariate analysis was performed to identify variables related to RI. A logistic regression model testing the outcome of RI was created by using statistically significant variables from the univariate analysis.

RESULTS

Patient Population

Preoperative and operative variables during the 2 eras are shown in Table 1. The mean recipient age increased slightly from the early to the current era (49.3 ± 12.1 vs 52.2 ± 12.5 years, $P = .05$). Other variables, including sex, race, body mass index, and CMV status, were no different between the 2 eras. Recipient diagnoses had minor but significant differences during the eras. α-1 Antitrypsin and primary pulmonary hypertension (PPH) were more common diagnoses in the early eras. Operative factors, including the use of CPB and the incidence of double LTX, were similar. Graft ischemic times significantly increased from the early era (223.3 ± 78.5 vs 286.3 ± 88.3 minutes, $P = .0001$). Comparing the early era with the current era, OI was not significant. The incidence of RI (as defined by an OI >7) was not different between the early and current eras (25% vs 22.6%, $P = .63$). Severe RI (as defined by an OI >10) was also not different between the groups (19.9% vs 16.1%, $P = .44$). The 30-day mortality for all lung transplant recipients significantly improved from 11.8% in the early era to 3.9% in the current era ($P = .003$).

Influence of RI on Early Mortality

RI remained the most important cause for early mortality, accounting for 81.3% (13/16) and 66.7% (4/6) of deaths in the early and current eras, respectively. The mortality of patients with RI significantly decreased from the early era compared with that seen in the current era (38.2% [13/34] vs 11.4% [4/35], $P = .01$, Table 2). Only 3 (2.2%) patients in the early era and 2 (1.3%) patients in the current era without RI died within 30 days of transplantation ($P = .67$).

TABLE 1. Patient demographics, diagnosis, and intraoperative factors in lung transplant recipients before and after March 2000

Recipient variables	Early era (n = 136)	Current era (n = 155)	*P* value*
Recipient factors			
Age (y)	49.3 ± 12.1	52.2 ± 12.5	**.05**
Male sex	46.3% (69)	53.5% (83)	.63
African American	8.1% (11)	10.3% (16)	.51
BMI	24.1 ± 5.6	24.7 ± 4.3	.30
CMV mismatch	25.7% (35)	29.0% (45)	.53
Recipient diagnosis			
COPD	44.8% (61)	52.9% (82)	.17
α1-Antitrypsin	14.0% (19)	4.5% (7)	**.005**
IPF	9.6% (13)	9.0% (13)	.89
Sarcoidosis	8.1% (11)	9.0% (14)	.78
Cystic fibrosis	7.4% (10)	11.0% (17)	.29
Lymphangioleiomyomatosis	0.7% (1)	1.3% (2)	.99
Pulmonary fibrosis, other	0.7% (1)	0% (0)	.47
Primary pulmonary hypertension	10.3% (14)	3.2% (5)	**.02**
Operative factors			
Graft ischemic time	223.3 ± 78.5	286.3 ± 88.3	**.0001**
Required CPB	19.1% (26)	16.1% (25)	.50
Double lung transplantation	22.1% (30)	25.8% (40)	.46
Outcomes and mortality			
OI	8.7 ± 10.0	6.5 ± 8.3	.06
Significant RI (OI >7)	25% (34)	22.6% (35)	.63
Severe RI (OI >10)	19.9% (27)	16.1% (25)	.44
30-d Mortality	11.8% (16)	3.9% (6)	**.003**

Categorical data are listed as numbers (percentages). Continuous variables are listed as means ± standard deviation. *BMI*, Body mass index; *CMV*, cytomegalovirus; *COPD*, chronic obstructive pulmonary disease; *IPF*, idiopathic pulmonary fibrosis; *CPB*, cardiopulmonary bypass; *OI*, Oxygenation index. **P* values were determined by means of χ^2 analysis, the Fisher's exact test, and the Student's *t* test, where appropriate.

TABLE 2. Operative variables and outcomes in patients with reperfusion injury during the 2 eras

Variables	Early era (n = 34)	Current era (n = 35)	*P* value
Preoperative and operative variables			
Age (y)	44.5 ± 15.2	49.0 ± 14.1	.21
Obstructive lung disease	32.4% (11)	42.9% (15)	.37
Fibrotic lung disease	50% (17)	45.7% (16)	.20
Primary pulmonary hypertension	17.6% (6)	5.7% (2)	.15
Required CPB	41.2% (14)	34.3% (12)	.55
Double lung transplantation	47.0% (16)	68.6% (24)	**.02**
Treatment and outcomes			
Use of NO/epoprostenol	26.5% (9)	11.3% (4)	.11
Use of ECMO	29.4% (10)	34.3% (12)	.66
Graft ischemic time (min)	242.6 ± 25.4	318 ± 78.5	**.0001**
OI severity	24.5 ± 9.7	18.2 ± 7.4	**.01**
Mortality with RI	38.2% (13)	11.4% (4)	**.01**

Categorical data are listed as numbers (percentages). Continuous variables are listed as means ± standard deviation. *CPB*, Cardiopulmonary bypass; *NO*, nitric oxide; *ECMO*, extracorporeal membrane oxygenation; *OI*, oxygenation index; *RI*, reperfusion injury.

LTX

Patients with RI

Patients with RI in the early and current eras were compared (Table 2). No significant differences in age, diagnoses, or use of CPB were identified. Patients who had RI in the current era more commonly underwent double LTX. Supportive treatment, including the use of ECMO, NO, and epoprostenol (prostacyclin), was available during both eras. The use of pulmonary vasodilators (NO and epoprostenol) alone in patients not requiring ECMO was not significantly different between the early and current eras (26.5% [9/34] vs 11.4% [4/35], $P = .11$). The use of ECMO for patients with RI did not increase during the study period (early era: 29.4% [10/34] vs current era: 34.3% [12/35], $P = .66$). Graft ischemic times increased in patients with RI over time (242.6 ± 25.4 vs 318 ± 78.5 minutes, $P = .0001$). In patients with RI, the severity of OI improved from the early era compared with that seen in the current era (OI of 24.5 ± 9.7 vs 18.2 ± 7.4, $P = .01$).

Patients Treated with ECMO

The overall survival for patients with severe RI requiring ECMO was 50% [11/22]. These patients were compared by era (Table 3). The mortality of patients with RI after ECMO significantly improved from 80% [8/10] in the early era to 25% [3/12] in the current era ($P = .01$). In the early era all 5 patients with cystic fibrosis died, whereas 2 patients with chronic obstructive pulmonary disease (COPD) died. One of 2 patients with PPH died, and 1 patient with pulmonary fibrosis survived. In the current era 2 of 4 patients with pulmonary fibrosis died, and 1 of 2 patients with PPH died. The remainder of the patients survived ECMO. Preoperative and operative variables, including age, diagnoses, and use of double LTX, were not different during the 2 eras in patients treated with ECMO. Importantly, the time to institute ECMO did not change in the current era. However, the

TABLE 3. Operative variables in patients with reperfusion injury treated with ECMO

Variables	Early era (n = 10)	Current era (n = 12)	*P* value
Preoperative and operative variables			
Age (y)	41.2 ± 18.6	46.1 ± 12.2	.47
Obstructive lung disease	20% (2)	33.3% (4)	.65
Pulmonary fibrosis	10% (1)	33.3% (4)	.32
Cystic fibrosis	50% (5)	8.3% (1)	.06
Primary pulmonary hypertension	20% (2)	16.6% (2)	.99
Double lung transplantation	70% (5)	58.3% (7)	.13
Graft ischemic time (min)	270 ± 72.7	309.9 ± 64.2	.19
Factors related to ECMO			
Time to institute ECMO (h)	2.5 ± 3.7	4.2 ± 8.6	.57
Duration of ECMO (h)	89 ± 29.8	30.6 ± 8.0	**.0001**
Venoarterial ECMO	100% (10)	83.3% (10)	.48
Mortality	80.0% (8)	25.0% (3)	**.01**

Categorical data are listed as numbers (percentages). Continuous variables are listed as means ± standard deviation. *ECMO*, Extracorporeal membrane oxygenation.

TABLE 4. Variables related to patients with reperfusion injury after lung transplantation

Variable	Patients without RI (n = 222)	Patients with RI (n = 69)	*P* value
Recipient age (y)	52.1 ± 11.8	46.8 ± 14.6	**.002**
Male sex	52.2% (116)	58.0% (40)	.41
Graft ischemic time (min)	250.7 ± 67.7	281.0 ± 52.4	**.0007**
Double lung transplantation (%)	19.8% (44)	39.1% (27)	**.001**
Required CPB	11.3% (25)	37.7% (26)	**.0001**
Obstructive lung disease	63.1% (140)	37.7% (26)	**.0002**
Fibrotic lung disease	32.4% (72)	47.8% (33)	**.02**
Primary pulmonary hypertension	4.5% (10)	13% (9)	**.0001**
Preservation solution			
Perfadex	75.3% (64)	24.7% (21)	.23
Other	90.0% (18)	10.0% (2)	

Categorical data are listed as numbers (percentages). Continuous variables are listed as means ± standard deviation. *RI*, Reperfusion index; *CPB*, cardiopulmonary bypass.

TABLE 5. Multivariate analysis of variables related to reperfusion injury after lung transplantation

Variable	OR (95% CI)	*P* value
Recipient age (y)	0.99 (0.95-1.04)	.22
Graft ischemic time (min)	1.00 (0.99-1.01)	.22
Double lung transplantation (%)	0.54 (0.12-2.43)	.42
Required CPB	2.28 (0.72-7.16)	.16
Obstructive lung disease	1.17 (0.37-3.70)	.79
Fibrotic lung disease	3.24 (0.81-12.99)	.10
Primary pulmonary hypertension	13.44 (1.13-159.27)	**.04**

OR, Odds ratio; *CI*, confidence interval.

duration of ECMO was significantly shorter in the current era (89 ± 29.8 vs 30.6 ± 8.0 hours, $P = .0001$). Venoarterial ECMO was preferred in both eras to treat RI. Central cannulation of the aorta and right atrium was preferred in cases of double LTX requiring postoperative ECMO, whereas femoral cannulation was the preferred technique after single LTX. Pulmonary blood flow is maintained to some degree with pulsatile flow through the pulmonary artery because bronchial blood flow is interrupted in transplanted lungs. Currently, during ECMO, minimal ventilator settings are used to avoid secondary ventilator-induced lung injury, patients are diuresed aggressively, and frequent pulmonary toilet is performed with bronchoscopy.

Correlation of OI with ISHLT Criteria

A P/F ratio was able to be computed during the current era. Grade 0 or 1 PGD occurred in 60% (93/155). Grade 2 and 3 PGD occurred in 16.8% (26/155) and 23.2% (36/155), respectively. Patients with grade 3 PGD were compared with patients with OIs of greater than 7. All but 5 patients met both criteria. Three patients with grade 3 PGD did not have an OI of greater than 7, and 2 patients with an OI of greater than 7 had grade 2 PGD per ISHLT definitions. Importantly, all patients who required ECMO during the current era had RI by either criterion. One patient with severe RI (by both criteria) died without ECMO. The 30-day mortality of Grade 3 PGD in the current era was 11.1% (4/36).

Risk Factors Related to RI

Several variables were evaluated to determine risk factors related to RI (Table 4). A total of 69 patients during the study period had RI. Sex did not correlate with RI; however, patients with RI were younger. Risk factors associated with RI included longer graft ischemic time, double LTX, fibrotic lung disease, and PPH. Of 19 patients with PPH during the study period, 8 had RI, and 4 required ECMO. Patients with obstructive lung disease were negatively correlated with RI. The use of Perfadex as a preservation solution was not associated with RI by means of univariate analysis (Table 4). A multivariate analysis was performed in an attempt to identify independent predictors of RI (Table 5). Variables included in the model were those that were found to have statistically significant associations with the outcome on univariate analysis. The model demonstrated modest statistical performance (c-statistic = 0.665, $R^2 = 0.046$). Only PPH (odds ratio, 13.44; $P = .04$) was found to be an independent predictor of RI.

DISCUSSION

RI still occurs in 20% to 35% of lung transplant recipients.[1,2] In the present report the incidence of RI as defined by OI was 22.6% in the current era and was not significantly less than that in the early era. We noted that the severity of RI improved during the current era, a finding that is consistent with other reports. Whitson and colleagues[7] reported that the severity of RI defined by grade 3 PGD decreased over time from 44% (1992–1998) to 27% (1999–2004).

It has been our observation that early mortality after LTX is improving. Historically, RI has had an associated mortality as high as 40% in some series,[8] but more recent reports suggest mortality rates have decreased to 14% to 17% at 90 days.[7,9] In our current era we report 30-day mortality rates of 1.8% and 3.9% for lung transplant recipients after 2006 and for those patients with RI, respectively. There are several potential explanations for these findings. Over the last 2 decades, several refinements in graft preservation and surgical technique have been developed and adopted. These pre-emptive approaches have been discovered to reduce RI.

Pretreatment of the donor lung with prostaglandin E_1 before harvest became routine at our center during the early era. Although reports documented no effect on RI in a porcine single LTX model,[10,11] other studies have demonstrated that prostaglandin E_1 will dilate the pulmonary vasculature, decrease RI, and decrease inflammatory cytokines in the transplanted lung.[12,13] The choice of preservation solution has also changed with time. Several reports have documented superior preservation with low-potassium dextran

solutions (eg, Perfadex) compared with high-potassium solutions.[14-16] Despite conflicting reports that have been unable to identify protection from RI with these solutions,[17,18] our recent practice has been to solely use Perfadex, despite not finding evidence of protection from RI in the present study. Avoidance of lung hyperinflation during harvest and lung storage in a canine transplant model has also been shown to minimize lung injury.[19] Controlled gradual reperfusion of the implant has been suggested as a measure to potentially decrease mechanical disruption of the pulmonary vascular endothelium and prevent RI[20-22]; this has become our standard technique to reperfuse the implant. Previously, we reported less acute rejection and bronchiolitis obliterans with the use of daclizumab compared with ATGAM.[23] Although RI was not evaluated in our previous study, ATGAM was not administered to patients with evidence of RI. Thus it is unlikely that the induction agent would have an effect on RI.

In cases in which RI is diagnosed, supportive treatments include cautious fluid management, diuresis, and avoidance of ventilator-induced injury. The superiority of low-volume ventilation is supported by the Acute Respiratory Distress Syndrome Network[24] and likely applies to transplanted lungs as well. Inhaled NO and prostacyclin have been demonstrated to decrease pulmonary artery pressure and improve the P/F ratio.[25,26]

When these therapies are insufficient, ECMO can benefit selected patients. Our preferred approach is venoarterial ECMO either in the chest or through femoral access because of concomitant right-sided heart dysfunction from associated pulmonary hypertension. Meyers and associates[27] reported a 58.3% survival to discharge after the use of ECMO, which is similar to the current findings. We previously reported that early institution of ECMO (within 2 hours) might be beneficial to successfully treat RI.[4] Importantly, the initiation of ECMO was not more expeditious in the current era and cannot explain our results. Our preferred technique of ECMO is central cannulation when possible to ensure oxygenated blood is being delivered to the heart and brain. It is likely that a combination of less severe RI, judicious ventilator management, and program maturation might explain our improved survival with RI and ECMO.

Variables related to RI by means of univariate analysis included graft ischemic time, double LTX, and the diagnoses of fibrotic lung disease and PPH. Except PPH, there is much controversy in the literature regarding risk factors for PGD.[28,29] The significance of graft ischemic time has been debated.[29] Inverse correlation of COPD with RI has been previously reported.[28]

Limitations

There are several limitations inherent to any single-institution report. The definition of RI used in this study was OI and not P/F ratio, as recommended by the ISHLT Working Group. In this report OI was used as a surrogate because our method of stratification in the early era was based on OI and not P/F ratio. The P/F ratio can be inaccurate in determining the severity of PGD in patients who are not intubated.[30] Nonetheless, the ISHLT Working Group has recently supported using P/F ratio to define the grade of RI.[31]

Second, the number of patients with RI is admittedly small, as is the number of patients requiring ECMO. Patients with RI in the 2 eras did have minor differences. Double LTX was more common and graft ischemic times were longer in the current era. PPH was also more common in the early era. However, patients with PPH who had RI or required ECMO were few, and this did not explain the differences in mortality seen between eras. Thus differences in patient groups alone do not explain the reduction in severity of RI or improved mortality.

CONCLUSION

Improved early survival after LTX is due to several factors. In the present era lung RI is less severe, likely because of several improvements in preservation and surgical techniques, as noted above. The treatment of PGD has also improved, with better survival seen with ECMO. Collectively, these findings help explain our improved early and 1-year survival after LTX.

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Discussion

Dr Shaf Keshavjee *(Toronto, Ontario, Canada).* Dr Ailawadi, that was a very nice presentation. I would like to congratulate your group on demonstrating significant improvements in the outcome of LTX in your center.

Although you have very eloquently explained why you use the old term ''reperfusion injury'' and the OI for comparison of your era outcomes, I think it is very important for the audience to recognize that we need to move toward standardizing nomenclature and measurement parameters for comparison if we are going to make meaningful observations in our patients.

I was quite pleased to see in your presentation the reference to the PGD grading system in your current-era patients. The ISHLT Working Group defined PGD to refer not only to RI but to acknowledge the fact that much of the syndrome of PGD that you see is related to donor factors, such as brain death, infection, aspiration, trauma, and so on, plus ischemia, reperfusion, and the immunologic factors in the recipient, and therefore that findings that you see related to improvement of this syndrome after transplantation might be attributed to many of the factors across the board. I particularly liked your comment about program maturation because it does speak to the attributable factor of increasing improvement in outcomes within the multidisciplinary teams that take care of these patients with increased volumes and increased experience. I do think that recipient factors do play a role in what you have seen because if you look at your data, the table does show that you have a net increase in lower-risk patients, patients with COPD and cystic fibrosis, and a net decrease in the higher-risk patients, patients with pulmonary hypertension and the idiopathic pulmonary fibrosis, and this certainly could contribute to outcomes, although you might have found that in your small sample size.

Therefore my questions are as follows. Do you know when your OPO instituted routine administration of steroids to the donors? This might be a factor in decreasing PGD.

Dr Ailawadi. I do not have the data back in the 1990s when that was initiated. I do know that it has been the routine in the current era.

Dr Keshavjee. That, again, was a transition that happened in the late 1990s in most organ procurement organizations (OPO), so that indeed could have been a factor.

Your study period spans from 1990 to 2006. You chose to split the eras at March 2000. Why did you choose that date? Second, your lung preservation solution, as you mentioned, went from Euro–Collins to University of Wisconsin solution to Perfadex. Did you look at your data separating Perfadex from the high-potassium solutions, and did you find anything interesting there?

Dr Ailawadi. That is a very good question. We chose March 2000 because that is when we analyzed our previous data and our last report had come out. That is when we first recognized that early initiation of ECMO might be beneficial. That might be an arbitrary date, but it is sort of when we made that last conclusion and realized that there might be a difference and became the transition point for this study. We did not analyze by preservation solution. Again, the transition point from Euro–Collins or University of Wisconsin solution started in 1999, and by 2000, we were exclusively using Perfadex, and that was almost superimposed with the March 2000 transition date. We can go back and look at how preservation solution related to RI.

Dr Keshavjee. I think for the purpose of the convenience of analyzing the database, it was probably easier, but it might be more meaningful to go back and look at that to see what role it played in your center.

In terms of the ECMO bridge to recovery, your mortality decreased from 80% to 25%, although the time to institution of

ECMO really did not change. To what do you attribute this improved outcome? Do you think that you are seeing a different form or more quickly recoverable form of PGD, or are there factors in your intensive care unit personnel that might have contributed to this improvement?

Dr Ailawadi. I think there are multiple potential explanations that are very difficult in this small sample size to really understand. I think that the way we handle the ventilator is much different now than it was in the 1990s based on the Acute Respiratory Distress Syndrome Network data. I think there is certainly a heightened awareness of RI or PGD in our intensive care unit, and they might not have been as aware in the early 1990s. I do think the severity of the injury to the lung is likely less severe now than it was in the 1990s. Even though we do not see that based on our incidence, I think the actual amount of injury to the lung has decreased, and we did try to show that when we analyzed the subgroup of patients that had RI, their OI was less.

Dr Keshavjee. You demonstrated a significant increase in PGD in the patients undergoing bilateral LTX. Do you think that this is real, or is it just that you are more able to diagnose PGD in the bilateral patients, whereas patients undergoing single LTX have the advantage of having the residual native lung to provide some function in some cases.

Dr Ailawadi. That might very well be the case. Obviously the ISHLT criteria were created for double LTC. It is difficult to tease that out. That is certainly a possibility.

Dr Keshavjee. Thank you very much.

Dr David M. Follette *(Sacramento, Calif)*. I have 2 questions. As we moved toward more aggressive use of marginal donors, donor management strategies changed and improved. Were there any changes in donor management strategies in your OPO that might have contributed to having better lungs going in? You mentioned one that we had talked about many years ago, which was the use of steroids, but there are other factors that might have contributed.

Dr Ailawadi. That is also a little bit difficult to tease out. Overall, I would say that we seem to be using a lot more marginal donors now than we have in the past. Our center has matured and has had experience with more marginal donors. I probably cannot say that there is anything that we can pinpoint that is different aside from OPO changes that have happened across the board at all institutions.

Dr Follette. We found in San Francisco that as we got better at taking care of marginal donors, we took even better care of the ideal donors.

The second question is the opposite approach of the last question our primary discussant asked. You used significantly more double LTXs in your second cohort, and perhaps some of us felt from Dr Patterson's teachings many years ago that double LTXs, well taken care of, might actually make the duration of your damage shorter. Do you think part of your excellent result is because you had a statistically significant increase in the number of double LTXs versus single LTXs?

Dr Ailawadi. It could be possible, although during the current era of the study period, only 25% of our LTXs were double LTXs, and therefore I am not sure whether I can draw that conclusion. This has currently changed at our institution within the last 3 years. More than 60% of our LTXs currently are double LTXs based on data from the ISHLT reports over the last several years, suggesting that there is a benefit.

Dr K. Robert Shen *(Rochester, Minn)*. Last year at this meeting, you had reported on less acute rejection, less bronchiolitis obliterans syndrome, and improved overall survival at your center after a change in the induction regimen from an ATG-based regimen to daclizumab. In your data were you able to assess the effect of the changes in the induction regimen in the 2 study periods? Do you have any comment on that?

Dr Ailawadi. The outcomes that we studied in that report were not 30-day mortality. They were long-term mortality, acute rejection, and bronchiolitis obliterans syndrome. We did not link those data with the 30-day data and PGD with this study. Furthermore, ATGAM is not given to patients with evidence of RI or PGD. I do not think the induction agent played an important role in RI.