THE PRESENCE OR SEVERITY OF SECONDARY PULMONARY HYPERTENSION DOES NOT AFFECT OUTCOMES FOR SINGLE LUNG TRANSPLANTATION

ON-LINE SUPPLEMENT

Supplemental Methods:

The grading of severity used in the manuscript was based on criteria from the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension, [1] and all patients were diagnosed as having World Health Organization (WHO) Group 3 pulmonary hypertension (PH). All patients met criteria for lung transplantation (LTX), [2] and lung allocation score (LAS) values were calculated for recipients who received transplants prior to implementation of the LAS system in 2005 using the variables that were available close to the time of transplantation to allow analysis of the LAS as a variable for the entire study population. Chronic lung allograft dysfunction (CLAD) was defined according to the International Society for Heart and Lung Transplantation (ISHLT) clinical practice guideline, [3] and primary graft dysfunction (PGD) was defined by 2006 ISHLT guidelines.[4] Graft survival was defined as either recipient death or graft loss requiring re-transplantation. We also examined whether using a cut point of 35 mm Hg to differentiate recipients with mPAP values ≥35 mm Hg (more severe PH) versus those with no or less severe PH (<35 mm Hg mPAP values) revealed a significant difference in Kaplan-Meier survival estimates.

Since 2008 all emphysema patients (COPD, alpha-1-antitrypsin deficiency) have been listed for bilateral lung transplant. This has been a reaction to less than optimal outcomes with single lung transplantation (SLT) primarily due to native lung hyperinflation issues as well as to literature suggesting improved outcomes in these patients after bilateral lung transplantation (BLT). We have felt that all fibrotic/ILD patients are candidates for SLT as well as BLT, regardless of pulmonary pressures. Older patients (>65 years) are heavily considered for SLT listing only. Other indications for SLT include small chest space, especially as an oversized single lung will have a good outcome with sidedness directed by quantitative perfusion scan. When using single lungs, the contralateral lung was not utilized in all instances. However, if the quality of the lung was acceptable, then it was used by our or another institution. No lungs meeting implant criteria were discarded.

Results Given in This Supplement:

Recipient demographics and characteristics are given in Tables 1-5. Supplemental Figure 2 depicts freedom from CLAD, and supplemental Figure 3 depicts long-term survival when a cut point of 35 mm Hg was used to differentiate recipients with more severe PH (mPAP ≥35 mm Hg) versus those with milder or no PH (mPAP <35 mm Hg).

Supplemental Discussion:

Many patients with advanced lung disease (ALD) will develop Group 3 PH as their disease progresses, and the presence of PH has been identified as a predictor of worse survival for patients with COPD or interstitial lung disease (ILD).[1,5-7] Long-term supplemental oxygen therapy may provide some benefit for patients with COPD and PH, [8,9] and oxygen is often administered but of unproven benefit for hypoxemic patients with other forms of ALD complicated by PH.[9] However, effective therapies to prolong survival, such as vasodilators that have been shown to benefit patients with primary pulmonary hypertension, have yet to be

identified for patients PH, and vasodilator therapy for PH may impair gas exchange by blunting hypoxic pulmonary vasoconstriction.[10]

Lung transplantation may be the only therapeutic option that can improve quality of life and prolong survival for patients with ALD, but the presence of associated PH as well as performing SLT have been identified as risk factors for complications such as primary graft dysfunction (PGD), which was found to significantly reduce one-year survival.[11] Although it has been suggested BLT may be a better choice of procedure type for patients with PH and mean pulmonary artery pressures (mPAP) greater than 40 mm Hg,[12] this opinion was made on the basis of a limited number of recipients transplanted for WHO Group 3 PH without a statistically significant advantage for BLT. Other investigators have not reported a significant difference in survival for SLT versus BLT in patients with PH.[13-16] Neurohr et al.[17] suggested that BLT may be preferable to SLT for IPF patients with PH, but patients with significantly elevated mPAP due to PH were preferentially given BLT.

Significant controversy remains regarding SLT in patients with ALD-associated PH, and single center studies that have been reported to date have analyzed data for relatively few recipients and have not stratified recipients with Group 3 PH who received SLT according to severity of their PH. Because preferentially performing BLT procedures in patients with SPH puts significant restraint on the donor lung pool and SLT can allow lungs from a single donor to benefit two recipients, we reviewed our experience with SLT for patients without SPH and those with mild, moderate, or severe PH to determine whether outcomes are significantly affected by the presence and severity of PH when SLT procedures are performed. Our findings suggest that SLT is both safe and effective in patients with PH and that the presence of PH or the severity of PH does not have a significant adverse effect on long-term outcomes including long-term survival (Figure 1 in Main Document) and freedom from CLAD (On-line supplement; Figure 2). Furthermore, recipients with severe pre-transplant PH did not have worse outcomes than patients with normal PAP values. Additionally, when separating our patients into 2 cohorts defined as no or mild PH (mPAP <35 mm Hg) versus more severe PH (mPAP ≥35 mm Hg, long-term survival was not worse for the cohort with more severe PH (On-line supplement; Figure 3). Our results corroborate previous studies that reported no difference in survival after SLT in patients with coexisting PH.[12-15] However, our study is the first to examine the impact of different degrees of PH severity in patients undergoing SLT, has a longer time period of post-transplant follow-up, and examined a larger number of recipients than previously published single-center observational investigations, and our results suggest that SLT can be performed with reasonable safety in patients for whom SLT is an appropriate consideration even when candidates have relatively severe PH.

When survival rates in all of our cohorts are compared to United Network for Organ Sharing (UNOS) data, our survival outcome data match or exceed outcomes for SLT on a national level. The UNOS database reports an average survival of SLT patients of 84.2%, 60.7%, and 44.1% at one, three, and five years. We observed survival rates superior to the UNOS rates in all patient groups at three and five years. At one-year follow-up, post-transplant survival for our recipients (no PH = 84.6%; mild PH = 87.3%; moderate PH = 83.3%; severe PH = 85.0%) were at the level of the UNOS one-year survival data for SLT (84.2%), and there were no statistically significant differences in one-year survival among our PH severity cohorts at one year.

In addition to the lack of difference in short- and long-term survival for our SLT recipients without PH versus those with PH, our current study also failed to identify major differences in peri-operative events. A major concern in performing SLT in patients with PH, especially when severe PH is present, is the theory that the increased native lung hemodynamic pressures will promote hyper-perfusion of the newly implanted lung and increase the risk of developing PGD.[1] Because of this concern, many centers preferentially perform bilateral transplants in all patients with PH [13,17-19] Although we observed a higher rate of ECMO and NO utilization in the severe PH cohort, we did not identify any differences in rates or severity of PGD among our recipient cohorts, including those with the most severe SPH (Table 4). Additionally, we did not observe significant differences in duration of assisted ventilation, ICU length of stay, and overall hospital length of stay.

A relative lack of donor lungs is a continuing problem that significantly limits our ability to transplant waitlisted candidates, and new strategies to both increase the donor organ pool and optimally utilize donated lungs are much needed. Methods that seek to increase lung donations have been proposed. These include a point-based system in Israel that rewards potential donors by enhancing their likelihood of receiving a donated organ themselves should they eventually need one themselves; this policy has led to an increase in registered donors.[20] A policy of "opting out" instead of the current "opting in" system continues to be evaluated in the United States as one method of increasing the number of registered donors.[21] Other measures include utilizing living donors for lobar lung transplants, increased usage of donation after cardiac death donor organs, accepting donors with a significant smoking history, increased use of donors older than 55 years of age, and using *ex vivo* lung perfusion to reclaim and rehabilitate marginal donor lungs.[22-27] Our study suggests that SLT can be considered for patients with PH rather than preferentially performing BLT on these patients, thereby increasing organ availability without compromising outcomes. Indeed, in COPD, there is evidence to suggest that a policy of SLT improves access to organs for other potential recipients without significant increase in post-transplant mortality.[28,29]

Limitations of our study include its observational, retrospective analysis of non-randomized patients and the potential selection bias introduced for patients selected for SLT. Another concern is the prolonged period of 14 years. Although this has the advantage of accruing a considerable number of recipients for our analyses and a long follow-up period for many of our patients, many changes have occurred including implementation of the LAS, which has had the effect of changing the primary indication for transplantation from COPD to IPF at our institution as well as worldwide.[30] We and others have observed that patients with IPF listed for transplantation following implementation of the LAS were generally older, had greater requirement for supplemental oxygen, had lower cardiac index values, and had more comorbidities.[31] This trend is likely to continue, especially with the recent candidate selection criteria update that suggests that candidates up to 75 years of age can be considered for transplant.[32] Many of these individuals are likely to have IPF, which is frequently accompanied by a moderate to severe degree of PH.[6]

In conclusion, patients with ALD-associated WHO Group 3 PH, regardless of severity, who underwent SLT at our center had no significant differences in immediate postoperative outcomes, incidence of CLAD, or long-term survival when compared to patients without evidence of PH. We suggest that PH should not by itself be considered to be a contraindication to SLT, which has the added benefit of expanding a limited lung donor pool and allowing lung

blocks to be split such that two recipients can receive lungs from a single donor. Future studies will be aimed at validating these results in a prospective fashion, and analysis of a large database, such as that of the United Network for Organ Sharing, may help to identify whether SLT should or should not be performed in patients with WHO Group 3 PH.

Supplemental Table 1. Pre-Transplant Recipient Characteristics.

Pre-operative Characteristics (mean values)	Pulmonary Hypertension Severity				*p* value
	None	Mild	Moderate	Severe	
N	150	55	54	20	--
Male gender (%)	71	67	80	65	0.78
Mean age (years)	58	57	57	58	0.66
Diabetes (%)	27	24	22	30	0.57
History of smoking (%)	75	82	78	65	0.64
Coronary artery disease (%)	9	20	17	5	0.045
Congestive heart failure (%)	5	4	4	15	0.10
Systemic hypertension (%)	36	38	39	55	0.26
Race = Caucasian (%)	93	98	87	70	0.006
Body mass index (kg/m^2)	25.6	26.0	26.7	26.7	0.44
Mechanical ventilation (%)	13	11	11	10	0.97
Supplemental oxygen use (L/min)	3.6	3.6	4.3	3.7	0.38
FVC (% predicted)	51.4	46.1	47.9	43.6	0.083
FEV1 (% predicted)	40.1	31.3	36.5	44.4	0.024
Lung allocation score (LAS)	38.1	37.2	42.9	47.5	<0.001
Time on waitlist (days)	286	348	281	81	0.009
Serum creatinine (mg/dL)	0.91	0.92	1.00	0.96	0.033
PCWP (mm Hg)	10	16	16	15	<0.001
Cardiac index ($L/min/m^2$)	2.8	2.9	2.7	2.8	0.41
Systolic PAP (mm Hg)	31	39	50	72	<0.001
Diastolic PAP (mm Hg)	14	21	23	33	<0.001
Mean PAP (mm Hg)	21	29	44	46	<0.001

FEV1 = forced expiratory volume in one second; FVC = forced vital capacity; PAP = pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure

Supplemental Table 2. Transplant Indications (Primary Disease).

Primary Disease (transplant indication)	Pulmonary Hypertension Severity				*p* value
	None	Mild	Moderate	Severe	
All recipients (N)	150	55	54	20	--
COPD/emphysema – N (%)	51 (34)	28 (51)	17 (32)	1 (5)	NS
Idiopathic pulmonary fibrosis – N (%)	68 (45)	14 (26)	22 (41)	10 (50)	NS
COPD with AATD – N (%)	10 (7)	8 (15)	2 (4)	0	<0.0001
Sarcoidosis – N (%)	3 (2)	1 (2)	3 (6)	6 (30)	NS
Hypersensitivity pneumonitis (N/%)	4 (3)	0 (0)	2 (4)	2 (10)	NS
Other (N/%)	14 (9)	4 (6)	8 (13)	1 (5)	NS

AATD = alpha-1-antitrypsin deficiency; COPD = chronic obstructive pulmonary disease

Supplemental Table 3. Donor Age and Recipient Intra-operative Characteristics.

Primary Disease (transplant indication)	Pulmonary Hypertension Severity				*p* value
	None	Mild	Moderate	Severe	
Donor age (years)	32	30	32	40	0.103
CPB required (%)	15	15	30	65	<0.001
CPB duration (minutes)	116	170	186	142	0.109
Ischemic time (minutes)	313	343	307	289	0.276
sPAP (mm Hg)	41	41	51	67	<0.001
mPAP (mm Hg)	29	29	35	47	<0.001

CPB = cardiopulmonary bypass; sPAP = systolic pulmonary artery pressure; mPAP = mean pulmonary artery pressure

Supplemental Table 4. Post-operative Recipient Characteristics.

Pre-operative Characteristics (mean values)	Pulmonary Hypertension Severity				*p* value
	None	Mild	Moderate	Severe	
PGD Grade 0-1 (%)	82	80	78	70	0.325
PGD Grade 2-3 (%)	18	20	22	30	
ECMO (%)	4	7	0	10	0.045
Nitric oxide use (%)	40	49	70	80	<0.001
Length of ventilation (days)	3.0	4.5	2.8	2.4	0.652
Prolonged ventilation >48 hrs (%)	26	27	32	20	0.704
ICU length of stay (days)	6.3	10.7	8.0	4.3	0.163
Hospital length of stay (days)	22	23	25	16	0.390
Readmission within 30 days (%)	17	35	17	25	0.097
30-day mortality (%)	5	2	4	5	0.831

ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; PGD = primary graft dysfunction

Supplemental Table 5. Cox Multivariate Analysis of Risk Factors for Death.

Variable	HR (95% CI)	p-value
Age	1.045 (1.014-1.076)	0.004
Waiting list time	1.000 (0.999-1.001)	0.78
Lung allocation score	1.009 (0.988-1.031)	0.41
Serum creatinine	1.273 (0.547-2.962)	0.58
FEV1 (% predicted)	1.012 (1.003-1.021)	0.01
PCWP	1.011 (0.982-1.040)	0.48
Mild PH	1.062 (0.673-1.676)	0.80
Moderate PH	0.919 (0.7536-1.577)	0.76
Severe PH	1.137 (0.527-2.452)	0.74

FEV1 = forced expiratory volume in one second; PAP = pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; PH = hypertension

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