AUDIT, RESEARCH AND GUIDELINE UPDATE

The presence or severity of pulmonary hypertension does not affect outcomes for single-lung transplantation

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ABSTRACT

Advanced lung disease (ALD) that requires lung transplantation (LTX) is frequently associated with pulmonary hypertension (PH). Whether the presence of PH significantly affects the outcomes following single-lung transplantation (SLT) remains controversial. Therefore, we retrospectively examined the outcomes of 279 consecutive SLT recipients transplanted at our centre, and the patients were split into four groups based on their mean pulmonary artery pressure values. Outcomes, including long-term survival and primary graft dysfunction, did not differ significantly for patients with versus without PH, even when PH was severe. We suggest that SLT can be performed safely in patients with ALD-associated PH.

INTRODUCTION

The presence of group 3 pulmonary hypertension (PH) in patients undergoing lung transplantation (LTX) for advanced lung disease (ALD) has been identified as a risk factor for complications such as primary graft dysfunction (PGD), which can significantly reduce 1-year survival rate.[1] Although it has been suggested that bilateral LTX (BLT) may be a better choice of procedure type for patients with ALD-associated PH and mean pulmonary artery pressure (mPAP) values >40 mm Hg,[2] other investigators have not reported a significant difference in survival for single-lung transplantation (SLT) versus BLT in patients with ALD-associated PH.[3] SLT offers the benefit of treating more patients with a scarce resource as well as making sure that single lung offers do not go to waste. At our own centre, we have not considered PH to be a contraindication to SLT, and when appropriate for other patient factors such as their primary disease process, we have used SLT in these patients. Therefore, we examined our immediate and long-term outcomes for SLT recipients with and without ALD-associated PH.

METHODS

This investigation was approved by the University of Wisconsin Human Subjects Committee (approval number M-2009-1308). Outcomes of 296 consecutive patients (none with a LTX indication of cystic fibrosis or primary PH) who underwent SLT between 1999 and 2013 were collected prospectively and analysed retrospectively. Eleven recipients were excluded due to retransplantation as their transplant indication, and six lacked PAP values. The remaining 279 patients were split into four groups based on right heart catheterisation (RHC) mPAP values (no PH (mPAP <26; N=150), mild PH (mPAP 26–40; N=55), moderate PH (systolic pulmonary artery pressure (sPAP) 45–59 or mPAP 41–55 mm Hg; N=54), and severe PH (sPAP >60 or mPAP >55 mm Hg; N=20)): grading of severity was based on criteria from the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension.[4] All subjects had at least one RHC, and when multiple RHCs were performed, the RHC value that was closest to the time of surgery was used. Mean time from preoperative RHC to LTX was 336 days. Lung allocation score (LAS) values were calculated for recipients transplanted prior to implementation of the LAS system in 2005.

Categorical data were summarised with frequency distributions and percentages. The mean ±SD values were calculated for variables that were normally distributed, and medians with interquartile ratios were presented for variables that were skewed. Continuous variables were compared using unpaired t test or non-parametric Mann–Whitney U test, whereas nominal variables were compared using χ^2 or the Fisher's exact test (as appropriate). The Kaplan–Meier method was used to assess lung graft survival and freedom from chronic lung allograft dysfunction (CLAD). Log-rank tests were used to assess statistical significance in survival and freedom from CLAD differences. Cox regression methods were used for multivariate analysis. A p value <0.05 (two-sided) was considered to be statistically significant. All analyses were performed using the SPSS statistical software program for Windows V.19.0 (SPSS, Chicago, Illinois, USA).

RESULTS

Baseline characteristics

Pretransplant characteristics of the study groups are given in the online supplementary table S1. A significantly higher LAS value (47.5) for the severe PH cohort correlated with decreased time on the waiting-list (81 days) compared with the other three groups. There was a statistically significant difference in the indication for LTX among the four groups (p<0.0001, online supplementary table S2). Patients without PH, mild PH or moderate PH were more likely to have a diagnosis of

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COPD (34%, 51% and 32%, respectively) than the group with severe PH (5%).

Intraoperative characteristics and early postoperative outcomes

There was a significant difference in rates of cardiopulmonary bypass (CPB) usage (see online supplementary table S3), which was significantly higher for the severe PH cohort (65%) versus all other groups (15% (no PH), 15% (mild PH), 30% (moderate PH); $p<0.001$)), but the length of CPB was no different between groups. Postoperatively, patients with moderate and severe PH had a higher rate of nitric oxide (NO) use (70% and 80%; online supplementary table S4) compared with patients without PH or mild PH (40% and 49%; $p<0.001$). The use of extracorporeal membrane oxygenation (ECMO) was minimal in all groups, and although patients with severe PH were the highest, patients with moderate PH were the lowest. Despite these increases in NO and ECMO use, important clinical factors such as length of ventilation, prolonged ventilation and severe PGD were no different among the four groups. Furthermore, there were no differences in 30-day mortality, length of stay or readmission among the four groups.

Long-term survival and freedom from CLAD

There were no differences in long-term survival among the four groups (figure 1), and the incidence of CLAD was similar for all groups (see online supplementary figure S2). Furthermore, after controlling for age, time on the waiting-list, LAS values, serum creatinine, FEV_1 per cent predicted and pulmonary capillary wedge pressure, the presence of mild, moderate or severe PH was not found to be associated with increased risk of death (see online supplementary table S5). Additionally, when we analysed long-term survival for all subjects using a mPAP threshold of 35 mm Hg, there was no difference in Kaplan-Meier actuarial survival between the two groups (see online supplementary figure S3).

DISCUSSION

Our results corroborate the previous studies that reported no difference in survival after SLT in patients with ALD and coexisting PH (see online supplementary material discussion). 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-centre observational investigations.

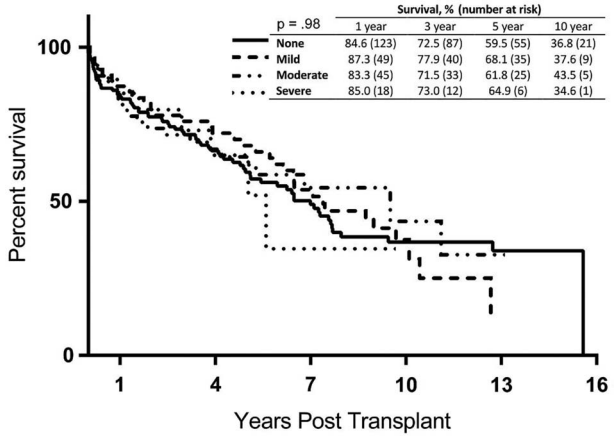

Figure 1 Long-term survival of single-lung transplant recipients with or without secondary pulmonary hypertension.

A major concern in performing SLT in patients with PH, especially when PH is severe, is the theory that the increased native lung haemodynamic pressures will promote hyperperfusion of the newly implanted lung and increase the risk of developing PGD.[4] Because of this concern, many centres preferentially perform BLT in all patients with PH. Although we observed a higher rate of NO usage in the severe PH cohort, we did not identify any significant differences in rates or severity of PGD, duration of assisted ventilation, intensive care unit (ICU) length of stay or overall hospital length of stay among our recipient cohorts. The increased rate of NO usage in this group is likely due to the fact that we aggressively use NO intraoperatively in most patients with PH, and NO is promptly discontinued postoperatively when the recipient has stabilised in the ICU. We have had a low threshold for using NO in SLT to maintain oxygenation and haemodynamics in patients with PH in preventive as opposed to salvage fashion, and most patients with elevated pulmonary pressures would have NO initiated prior to incision. Similarly, we routinely use CPB in all patients undergoing BLT, and it is frequently used for SLT recipients perceived to be at high risk of developing significant PGD. Cannulation is performed prior to implantation of the lung and CPB is initiated prior to reperfusion. The rate of ECMO usage in the severe group was also the highest; however, this may have been due to non-PH factors, as patients with moderate PH had the lowest rate of ECMO use and patients without PH were between the two groups. Most importantly, long-term survival was no worse in any of our PH groups compared with patients without PH; therefore, these minimal postoperative differences did not appear to have any clinical implications.

A relative lack of donor lungs is a continuing problem that significantly limits transplantation of candidates on the waiting-list, and new strategies to both increase the donor organ pool and optimally use donated lungs are much needed.[5] Our study suggests that SLT can be considered for patients with WHO group 3 PH rather than preferentially performing BLT, thereby increasing organ availability without compromising outcomes. Indeed, in COPD, there is evidence to suggest that a policy of using SLT improves access to organs for other potential recipients without a significant increase in post-transplant mortality.

Limitations of our study include its observational, retrospective design, the heterogeneity of recipients' lung disease diagnosis, the potential selection bias introduced for patients selected for SLT and the time span of 14 years. Implementation of the LAS, for one, has had the effect of changing the primary indication for transplantation from COPD to idiopathic pulmonary fibrosis (IPF) at our institution as well as worldwide. We and others have observed that patients with IPF listed for LTX following implementation of the LAS were generally older, had greater requirements for supplemental oxygen, had lower cardiac index values and had more comorbidities. 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. Many of these elderly individuals are likely to have IPF, which is frequently accompanied by a moderate-to-severe degree of PH.

In conclusion, patients with PH, even when severe, who underwent SLT at our centre had no significant differences in immediate postoperative outcomes, incidence of CLAD or long-term survival when compared with patients without evidence of coexistent PH. We suggest that PH should not by itself be

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considered to be a contraindication to SLT. This approach can help to expand a limited lung donor pool and allow lung blocks to be split such that two recipients can receive lungs from a single donor.

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Competing interests KCM has been an investigator in clinical trials sponsored by Abbott, Actelion, Altana, Amgen, Asthmatx, Bayer, Boehringer-Ingelheim, Bristol Meyers Squibb, Chiron, Discovery Labs, DuPont Merck, Fibrogen, Genentech, Gilead, GlaxoSmithKline, Inspire. InterMune, Johnson & Johnson, Novartis, Nycomed, Pfizer, Pharmaxis, PreAnalytiX, Roche, Ross, Vertex, and Wyeth. KCM has also served on a clinical advisory board for InterMune and serves on a clinical trial adjudication committee for Medimmune. All authors do not report any other relevant affiliations or financial involvement with any organisation or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. No writing assistance was used in the production of this manuscript.

Ethics approval University of Wisconsin Human Subjects Committee.

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