CARDIOTHORACIC TRANSPLANTATION

SECONDARY PULMONARY HYPERTENSION DOES NOT ADVERSELY AFFECT OUTCOME AFTER SINGLE LUNG TRANSPLANTATION

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Objective: Primary and secondary pulmonary hypertension have been associated with poor outcomes after single lung transplantation. Some groups advocate double lung transplantation and the routine use of cardiopulmonary bypass during transplantation in this population. However, the optimal procedure for these patients remains controversial. The goal of our study was to determine the safety of single lung transplantation without cardiopulmonary bypass in patients with secondary pulmonary hypertension. **Methods:** We retrospectively reviewed 76 consecutive patients with pulmonary parenchymal disease who underwent single lung transplantation from 1992 to 1998. Recipients were stratified according to preoperative mean pulmonary artery pressure. Secondary pulmonary hypertension was defined as parenchymal lung disease with a preoperative mean pulmonary artery pressure of 30 mm Hg or more. Patients with primary pulmonary hypertension or Eisenmenger's syndrome were excluded from analysis. **Results:** Eighteen of 76 patients had secondary pulmonary hypertension. No patient with secondary pulmonary hypertension required cardiopulmonary bypass, whereas 1 patient without pulmonary hypertension required bypass. After the operation, no significant differences were seen in lung injury as measured by chest radiograph score and $\text{PaO}_2/\text{FiO}_2$ ratio, the requirement for inhaled nitric oxide, the length of mechanical ventilation, the intensive care unit or hospital length of stay, and 30-day survival. There were no differences in the forced expiratory volume in 1 second or 6-minute walk at 1 year, or the incidence of rejection, infection, or bronchiolitis obliterans syndrome greater than grade 2. Survival at 1, 2, and 4 years after transplantation was 86%, 79%, and 65%, respectively, in the low pulmonary artery pressure group and 81%, 81%, and 61%, respectively, in the group with secondary pulmonary hypertension ($P > .2$). **Conclusion:** We found that patients with pulmonary parenchymal disease and concomitant secondary pulmonary hypertension had successful outcomes as measured by early and late allograft function and appear to have acceptable long-term survival after single lung transplantation. Our results do not support the routine use of cardiopulmonary bypass or double lung transplantation for patients with this disorder. (J Thorac Cardiovasc Surg 2000;119:458-65)

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Lung transplantation is a viable therapeutic strategy for patients with end-stage pulmonary parenchymal and vascular disease.¹⁻⁴ Controversy exists regarding the optimal procedure for patients with primary or secondary pulmonary hypertension (PHTN). Because of an elevated pulmonary vascular resistance (PVR) in the native lung, patients undergoing single lung transplantation (SLT) for pulmonary hypertensive disorders may not tolerate allograft reperfusion injury and may experience increased perioperative morbidity and death compared with patients without pulmonary hypertension. Long-term allograft function has also been reported to be suboptimal after SLT for PHTN.⁵ This has led some centers to recommend routine sequential double lung transplantation (DLT) and cardiopulmonary bypass (CPB) in patients with elevated preoperative pulmonary artery pressures (PAPs).^{5,7} Because earlier reports have dealt with either isolated pulmonary vascular disease or have combined patients with primary and secondary PHTN, these recommendations remain controversial for patients with secondary PHTN. We reviewed our experience to evaluate whether SLT in patients with moderate secondary PHTN can be performed safely without CPB.

Methods

Patient population and definition of secondary PHTN.

We retrospectively reviewed the case histories of 76 consecutive patients who underwent SLT for pulmonary parenchymal disease at the University of Colorado Health Sciences Center between July 1992 and June 1998. Patient characteristics and preoperative diagnoses are detailed in Table I. Recipients were stratified according to PAPs into high PAP or low PAP groups. Secondary PHTN was defined as the presence of parenchymal lung disease and a mean PAP of 30 mm Hg or more. Within the low PAP group (n = 58 patients), 28 patients had chronic obstructive pulmonary disease, 11 patients had α -1-antitrypsin deficiency, and 19 patients had idiopathic pulmonary fibrosis. Within the secondary PHTN group (n = 18 patients), 12 patients had chronic obstructive pulmonary disease, 1 patient had α -1-antitrypsin deficiency, and 5 patients had idiopathic pulmonary fibrosis. Patients with primary PHTN or Eisenmenger's syndrome were excluded from analysis.

Donor selection and perioperative management. Donors were evaluated and deemed acceptable on the basis of previously published criteria.¹³ Acceptable donor criteria included age less than 60 years, no history of pulmonary disease, P_{aO_2} greater than 300 mm Hg on an inspired oxygen fraction (F_{IO_2}) of 1.0 and a positive end-expiratory pressure of 5 cm H_2O , clear chest radiograph, negative sputum Gram stain, and an unremarkable bronchoscopic examination. Preservation of pulmonary allografts was performed with modified Euro-Collins solution and central venous alprostadil (prostaglandin E_1 ; 500 μ g) infusion. Recipients underwent standard pul-

monary function testing, echocardiography, right and left radionuclide ventriculography, and right heart catheterization before the transplantation. PAPs and right ventricular function were not used as exclusionary factors for SLT. Coronary arteriography was performed for candidates over 40 years of age. Donor lungs were matched to recipients by ABO compatibility, height and weight, and vertical and inframammary circumferential dimensions within 20% of the recipient dimensions. Operative techniques were as previously described.¹⁴

DLTs are not performed a priori for secondary PHTN at our institution but rather are chosen for the classic indication of septic lung disease or young patients with α -1-antitrypsin deficiency. CPB or inhaled nitric oxide is used only when mandated by hemodynamic instability, inadequate gas exchange, or technical difficulty.

Patients received standard triple-drug immunosuppression with cyclosporine (INN: ciclosporin), azathioprine, and prednisone and did not receive lympholytic agents for induction. Methylprednisolone (Solu-Medrol) 500 mg/kg was given intravenously immediately before allograft reperfusion, then 125 mg intravenously every 12 hours for 6 doses. Prednisone was then given at 1 mg/kg per day and tapered to 0.1 to 0.15 mg/kg per day by 1 month. Cyclosporine was maintained at trough levels of 350 to 450 ng/dL, and azathioprine was given at up to 2.5 mg/kg per day to maintain a whole white blood cell count of 5000 cells/ μ L.

Assessment of early allograft function. The degree of reperfusion injury was measured by chest radiography scores and gas exchange. Chest radiographs were obtained at 0, 24, and 48-hour intervals after the operation. The allograft was divided on chest radiograph into upper and lower halves, and each was scored as follows: 0, normal findings; 1, perihilar or localized infiltrate; and 2, diffuse moderate to severe interstitial and alveolar infiltrate. The halves were then added to give a chest radiography score of 0 to 4. Each radiograph was interpreted by a single radiologist at our institution who was blinded to the intent of the study. Arterial blood gases were obtained at 0 and 24 hours after the transplantation and used to calculate the P_{aO_2}/F_{IO_2} ratio. The need for postoperative inhaled nitric oxide, length of mechanical ventilation, intensive care unit and hospital length of stay, and patient survival at 30 days were recorded. Pulmonary hemodynamics were measured by balloon-tipped pulmonary artery catheter and compared with preoperative values.

Assessment of late allograft function. Postoperative forced expiratory volume in 1 second (FEV_1) and 6-minute walk distance were recorded at frequent intervals and reported at 1 year. The incidence of acute rejection episodes and infections was documented. The incidence of bronchiolitis obliterans of more than grade 2 was determined by routine postoperative pulmonary function tests or by its presence on transbronchial biopsy. Acute and chronic rejection were graded according to International Society for Heart and Lung Transplantation criteria.¹⁵ Survival was reported at 1, 2, and 4 years.

Statistical analysis. Preoperative and postoperative variables were compared with the use of analysis of variance and

Table I. Preoperative diagnoses and characteristics of 76 patients who underwent SLT ($P > .2$)

	Low PAP group (n = 58)	Elevated PAP group (n = 18)
Age (y)	50.6 ± 9.7 (26-69)	52.3 ± 6.1 (45-68)
M/F (n)	29/29	10/8
Allograft side, right/left (n)	21/37	7/11
Preoperative diagnosis (n)		
Chronic obstructive pulmonary disease (%)	28 (48)	12 (67)
α_1 -Antitrypsin (%)	11 (19)	1 (6)
Idiopathic pulmonary fibrosis (%)	19 (33)	5 (28)
Need for CPB/inhaled nitric oxide	1/1	0

Table II. Preoperative hemodynamic comparison and severity of PHTN in low and elevated PAP groups

	Low PAP group (n = 58)	Elevated PAP group (n = 18)
Systolic PAP (mm Hg)	30.1 ± 5.6	45.2 ± 3.6*
Range	14-37	38-56
Mean PAP (mm Hg)	18.5 ± 4.4	30.1 ± 4.4*
Range	9-29	30-39
Severity of PHTN (n)		
Mild†		0
Moderate‡		18
Severe§		0
PVR (dynes · sec · cm ⁻⁵)	192.2 ± 69.7	332 ± 65.2*

* $P = .001$.

†Mean PAP, 25-29.

‡Mean PAP, 30-39.

§Mean PAP, ≥40.

the Scheffé test. Results are stated as mean ± standard deviation. Survival and the incidence of acute and chronic rejection and infection were compared with the use of Kaplan-Meier analysis.

Results

Patient population and perioperative characteristics. Table I depicts the patient characteristics and their preoperative diagnoses. Table II depicts preoperative hemodynamic values and the severity of PHTN. We found that 18 patients had elevated PAPs and that 58 patients had low PAPs. Systolic and mean PAPs were significantly higher in the elevated PAP group than in the low PAP group (systolic PAP, 45.2 ± 3.6 mm Hg vs 30.1 ± 5.6 mm Hg, respectively; mean PAP, 30.1 ± 4.4 mm Hg vs 18.5 ± 4.4 mm Hg, respectively; $P = .0001$). PVR was significantly elevated in the high PAP versus the low PAP group (332 ± 65.2 dynes · sec · cm⁻⁵ vs 192.2 ± 69.7 dynes · sec · cm⁻⁵; $P = .001$). There were no significant differences between groups with regard to age, sex, or indication for transplantation. Among the 76 SLT recipients, 28 recipients received right lung allografts and 48 recipients received left lung allografts. A similar percentage in each group received right lung allografts. There were no intraoperative

deaths. CPB was used in 1 patient in the low PAP group because of intraoperative hemorrhage but was not required for any patient in the elevated PAP group. Inhaled nitric oxide was used intraoperatively in 1 patient in the low PAP group to avoid CPB.

Early and late allograft function. There were no significant differences in early allograft function measured by chest radiography injury scores (Fig 1, A), $\text{PaO}_2/\text{FiO}_2$ ratios (Fig 1, B), length of mechanical ventilation (50.8 ± 53.6 hours in the low PAP group vs 49.2 ± 54.1 hours in the high PAP group; $P > .2$), intensive care unit stay (80.0 ± 53.5 hours in the low group vs 77.3 ± 32.5 hours in the elevated group; $P > .2$), or hospital length of stay (14.6 ± 3.8 days in the low PAP group vs 11.9 ± 5.8 days in the elevated group). After the operation, systolic PAP and mean PAP fell significantly in the high PAP group (systolic PAP, 45.2 ± 0.9 mm Hg to 32.1 ± 1.6 mm Hg; mean PAP, 30.9 ± 1.0 mm Hg to 21.6 ± 1.4 mm Hg; $P < .004$; Fig 2). There were no significant changes in pulmonary pressures in the low PAP group (systolic PAP, 30.1 ± 0.7 mm Hg to 27.8 ± 0.7 mm Hg; mean PAP, 18.5 ± 0.6 mm Hg to 17.6 ± 0.5 mm Hg; $P > .2$). There was a significant fall in PVR in both groups after the transplantation (high PAP, 332 ± 65.2 dynes · sec · cm⁻⁵ to 206.1 ± 52 dynes

Fig 1. Comparison of early allograft function by postoperative chest radiography (CXR) injury scores (A) and Pao₂/Fio₂ ratios (B) between the low (black bar) and elevated (open bar) PAP groups ($P > .2$).

Fig 2. Postoperative change in systolic PAP (A) and mean PAP (B) in low and elevated PAP groups. * $P = .0001$ high vs low. ** $P = .0004$ vs preoperative value.

$\cdot \text{sec} \cdot \text{cm}^{-5}$; $P = .0001$; low PAP, 192.2 ± 69.7 dynes $\cdot \text{sec} \cdot \text{cm}^{-5}$ to 164.2 ± 41.5 dynes $\cdot \text{sec} \cdot \text{cm}^{-5}$; $P = .007$). Postoperative inhaled nitric oxide was used in 5 patients in the low PAP group (8%) and 2 patients in the elevated PAP group (11%) because of allograft dysfunction ($P > .2$). There were 2 early deaths in each group, yielding survivals at 30 days of 95% in the low PAP group and 89% in the elevated PAP group ($P > .2$). The overall incidence of acute rejection was 0.30 episodes per 100 patient-days in the low PAP group and 0.35 episodes per 100 patient-days in the elevated PAP

group ($P > .2$; Fig 3, A). Infection in the low PAP group was 0.30 episodes per 100 patient-days and 0.45 episodes per 100 patient-days in the high PAP group ($P > .2$; Fig 3, B). There were no significant differences in long-term allograft function as measured by FEV₁ and 6-minute walk distance at 1-year after the transplantation (Fig 4). Finally, bronchiolitis obliterans of more than grade 2 (diagnosed by pulmonary function test criteria or transbronchial biopsy) was found in 37% in the low PAP group and in 33% of the elevated PAP group ($P > .2$). Mean time to diagnosis of bronchiolitis oblit-

Fig 3. Comparison of incidence of acute rejection (A) and acute infection (B) in low (black bar) versus elevated (open bar) PAP groups ($P > .2$).

Fig 4. FEV₁ (A) and 6-minute walk (B) at 1 year in low (black bar) and elevated (open bar) PAP groups ($P > .2$).

erans syndrome (BOS) of more than grade 2 was 28.0 ± 4.7 months in the high PAP group and 26.3 ± 4.0 months in the low PAP group ($P > .2$; Fig 5).

Survival. The 1-, 2-, and 4-year survivals after transplantation for patients in the low PAP group were 86%, 79%, and 65% and in the elevated PAP group, 81%, 81%, and 61%, respectively ($P > .2$; Fig 6).

Discussion

Several groups have shown that SLT for PHTN is associated with increased morbidity and death and that long-term allograft function and survival may be suboptimal.^{4,8} This has led some centers to recommend

sequential DLT and the use of CPB in all patients with pretransplantation elevation of PAPs.^{5,7,9} Many of these previous reports dealt with primary PHTN or combined the outcomes of patients with primary and secondary PHTN into 1 group. When analyzed separately, patients with secondary PHTN have similar 12- and 18-month survivals compared with patients without PHTN.⁶ However, these patients may still have increased intraoperative and perioperative complications. Preliminary observations by Park and colleagues⁷ revealed that SLT, in patients with pulmonary parenchymal disease and elevated preoperative PAPs (systolic PAP ≥ 40 mm Hg), was associated with an 8.5-fold increase in the need for

Patients	Low	55	54	49	48	44
at Risk	High	15	15	15	15	13

Fig 5. Percentage of freedom from BOS of more than grade 2 in low (*dashed line*) and elevated (*solid line*) PAP groups ($P > .2$). Confidence limits: 1-year (low group, 0.97 to 0.78; high group, 0.96 to 0.76) and 3-year (low group, 0.77 to 0.46; high group, 0.86 to 0.66).

Patients	Low	55	52	48	47	47
at Risk	High	15	15	15	15	13

Fig 6. Survival curves by Kaplan-Meier method for low (*dashed line*) versus elevated (*solid line*) PAP groups ($P > .2$). Confidence limits: 1-year (low group, 0.95 to 0.77; high group, 1.0 to 0.62); 3-year (low group, 0.86 to 0.62; high group, 1.0 to 0.62); and 4-year (low group, 0.80 to 0.50; high group, 0.95 to 0.26).

CPB. Further, they found a markedly diminished 3-year survival of 34% versus 77% in patients without secondary PHTN. They concluded that secondary PHTN is an independent risk factor for diminished patient survival and the need for CPB. In the present study, we found that patients undergoing SLT for pulmonary parenchymal diseases with moderate PHTN did not have an increased requirement for CPB or early allograft dysfunction compared with patients with secondary PHTN. Further, we found no differences in long-term survival or allograft function between groups.

PHTN is associated with pulmonary vasoconstriction, vasoproliferation, and a subsequent increase in

PVR. After SLT, this increased PVR in the native lung diverts 85% to 100% of the perfusion to the allograft. Reperfusion injury may lead to increased ventilation-perfusion mismatching and gas exchange abnormalities compared with a similar degree of injury in patients who are able to more equally distribute pulmonary blood flow between the allograft and the native lung. For this reason, some consider SLT in the setting of PHTN to be contraindicated. However, Boujoukos,¹¹ and Sheridan,¹² and their colleagues have shown that preferential blood flow to the allograft does not in itself enhance reperfusion injury and that early and late allograft function is maintained. The present study also

supports the finding that, in the setting of PHTN, preferential blood flow to the allograft does not augment reperfusion injury and that the mechanism behind reperfusion injury in the setting of PHTN is multifactorial. Therefore routine use of DLT may not provide a significant early physiologic or functional advantage in patients with moderate PHTN.

There are a number of theoretic advantages of DLT over SLT for pulmonary hypertensive disorders. DLT provides more pulmonary reserve than SLT. Therefore patients in whom BOS develops after DLT may tolerate chronic rejection better than patients who undergo SLT. DeHoyos and colleagues² have also reported a possible increased incidence of BOS after SLT for PHTN. We did not find this to be the case in our patients. The incidence of and the time to onset of BOS were similar in both groups in our study. The incidence of BOS may in fact be identical in SLT versus DLT but may be detected earlier in SLT patients because of the smaller pulmonary reserve. This same group also reported decreased long-term survival in SLT versus DLT for PHTN. The advantages of SLT over DLT are shorter ischemia times and maximal use of available donor lungs. The present study was not designed to compare the outcomes of SLT versus DLT for PHTN.

Gammie and colleagues⁶ have recently reported that, in their 8-year experience of SLT versus DLT for primary and secondary PHTN, they found similar mortality and long-term outcomes in each group. Although theirs is not a randomized trial, they cautiously supported the use of SLT for patients with PHTN. A significant difference between their experience and ours is the apparent routine use of CPB for all patients with underlying PHTN. CPB during lung transplantation may itself lead to allograft injury. Aeba and colleagues¹⁰ demonstrated these undesirable effects in patients who underwent SLT or DLT for a variety of underlying conditions. They concluded that the use of CPB led to impaired oxygenation, prolonged intubation, enhanced lung injury, and diminished 1-month survival. Therefore the avoidance of CPB may provide substantial benefit to patients in regard to limiting reperfusion injury, postoperative hemodynamic stability, ease of extubation, and overall allograft performance. We use bypass only if mandated by hemodynamic instability, inadequate gas exchange, or technical difficulty during the operation. We have also found that inhaled nitric oxide may be effective in preventing the need for CPB during an operation.

The discrepancy between our results and those of other centers may be due to the fact that we only reviewed patients with secondary PHTN of a moderate level, whereas earlier reports included patients with

both primary and secondary PHTN. These groups may not be directly comparable. Pathologically, primary PHTN is associated with plexogenic arterial lesions, and secondary PHTN is associated with predominantly vascular smooth muscle cell proliferation. Physiologically, when compared with secondary PHTN, primary PHTN is associated with a more rapid progression, a more severe decrease in right ventricular ejection fraction, and a more severe fall in cardiac output with exercise. Finally, patients who undergo transplantation for primary PHTN typically have near-systemic PAPs and mean PAPs in excess of 50 to 60 mm Hg. All of our patients with secondary PHTN had mean PAPs between 30 and 40 mm Hg and would be classified as having moderate PHTN. Alternatively, the difference may be due to the low number of patients in our elevated PAP group ($n = 18$ patients). A type II (β) error may be present, and we are unable to detect a difference between these groups at this time. However, in a similar-sized group of patients with secondary PHTN, Park and colleagues⁷ found markedly different results than ours. Perhaps there are other unstated differences in donor and recipient selection or in intraoperative and postoperative management strategies that account for the observed differences between their study and ours. Finally, the lack of prospective randomization of patients to SLT versus DLT with or without the use of CPB could have introduced inherent bias into this study.

In summary, we found that patients with pulmonary parenchymal disease and concomitant secondary PHTN have successful outcomes regarding early and late allograft function and appear to have acceptable long-term survival after SLT. Our results do not support the routine use of CPB or DLT in patients with secondary PHTN. The use of SLT in this patient population not only provides adequate outcomes but also makes maximal use of the available donor pool by limiting the use of DLT to younger patients or those with septic lung diseases who have no other alternatives in the choice of lung transplantation procedure.

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Discussion

Dr Vaughn A. Starnes (*Los Angeles, Calif*). One of the things that I have taken away from this article is trying to redefine what is meant by secondary PHTN. We see excellent results in a group of patients who had primary parenchymal lung disease and some resulting mild hypertensive changes in a small group of those patients. As we look at this issue, and this topic has been discussed in the literature for 5 to 6 years, the implication when I first saw the title was that PHTN did not affect the need for DLT. At the end of the article, I felt as if SLT was an effective therapy for parenchymal lung disease.

What was the PVR in this group of patients in the moderate hypertensive group? Did you look at any of these results in a postoperative period of time as it relates to perfusion scanning; that is, did the allograft have most of the perfusion going to it or a balance of perfusion, as would be indicated by your $\text{Pao}_2/\text{Fio}_2$ ratio?

The whole issue concerning SLT for primary or secondary PHTN has been in the area of a vascular lesion and not a parenchymal lung lesion. That is really what we are dealing with today, a parenchymal lung lesion.

Dr Huerd. We did measure the PVR in each patient preoperatively but did not routinely evaluate changes in PVR over time. To answer your question regarding the evidence of equivalent gas exchange based on our pulmonary function and perfusion studies between the two sides, we did not rou-

tinely follow up on those patients with perfusion scans to determine whether our allograft received 50%, 70%, or 90% of the flow. We did make the assumption that because their pressures were lower than what you would see in a patient with primary PHTN, the flow would probably be equivalently distributed between the two lungs and that the native lung significantly participated in gas exchange postoperatively.

Dr Starnes. Did you know whether these patients had PHTN preoperatively? If so, did that prejudice your donor selection for these particular recipients?

Dr Huerd. No. On the basis of our preoperative evaluation of each patient, we did know their preoperative PAP, and that knowledge did not change our donor selection criteria.

Dr Thomas M. Egan (*Chapel Hill, NC*). I thought everyone in Denver had PHTN, and I raise the issue because I am curious as to what proportion of patients who undergo lobectomy for lung cancer or some other pulmonary resection would have PAPs in that range. I would not think that you would define that PAP as being so unusual in Denver.

What would you do with someone with pulmonary fibrosis with a PAP of 80/50 mm Hg and a mean of 65 mm Hg? You did not have any patients with severe PHTN, but many of the patients whom we see with pulmonary fibrosis, and in particular sarcoidosis, have significant elevation of PAP. What do you do with those patients?

Dr Huerd. I do not believe everyone in Denver has elevated PAPs. What we see routinely is that the PAPs in patients in Denver are exactly the same as anywhere else and that there have been no data from our institution that have shown that patients at a higher elevation have a higher inherent pressure.

To answer your question about someone with idiopathic pulmonary fibrosis and a mean PAP of 65 mm Hg, we actually would consider that patient with a mean PAP above 60 mm Hg to have enough elevated pressures that we would proceed with a DLT in that particular population. We were focusing mostly on patients who have what we would consider moderate secondary PHTN, and based on recent abstracts that have been submitted, we believe that it is really not an independent variable to predict a poor outcome for a patient who undergoes an SLT.

Dr Walter Klepetko (*Vienna, Austria*). You have mentioned a higher infection rate in the patients with secondary PHTN. However, this difference did not reach statistical significance. Have you done any analysis as to whether these infections derived from the native lung or the transplanted lung? One could assume that the native lung in patients with moderate PHTN who have undergone transplantation will receive less pulmonary blood flow than the transplanted lung and therefore might be more susceptible to infection.

Dr Huerd. No, we have not looked specifically at the source of the infection, but we would infer, based on what Dr Starnes had commented on earlier, that flow between the allograft and the native lung is probably equally distributed since our mean pressures were in the 30 to 39 mm Hg range. I would assume that flow would be nearly equivalent between the two sides and that we could not predict higher native lung infection rates.