CARDIAC AND PULMONARY REPLACEMENT

SINGLE- VERSUS DOUBLE-LUNG TRANSPLANTATION FOR PULMONARY HYPERTENSION

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Objectives: Uncertainty persists as to the best lung transplant operation for patients with pulmonary hypertension. To quantify short- and long-term outcomes after single- and double-lung transplantation for pulmonary hypertension, we reviewed our clinical experience. **Methods:** A retrospective review of 58 lung transplants at a single institution between 1989 and 1996 was performed. Recipients had primary ($n = 19$) or secondary ($n = 39$) pulmonary hypertension. **Results:** Thirty-seven double- and 21 single-lung transplants were performed. The groups were well matched with regard to preoperative characteristics. Cardiopulmonary bypass time was longer (151 vs 250 minutes) in the double-lung group. Excluding 10 patients surviving less than 30 days (6 double- and 4 single-lung transplants), median duration of intubation (7.5 vs 10 days), length of stay in the intensive care unit (10 vs 16 days), and hospital stay (32 vs 52 days) were not significantly different for the single- and double-lung groups, respectively. Actuarial survival was nearly identical, with 81% and 84% 1-month survivals for the single- and double-lung groups, and identical 1-year (67%) and 4-year (57%) survivals for both groups. Late functional status was similar for recipients of single- and double-lung grafts. During the period of this study, 58 patients with pulmonary hypertension died on our center's waiting list before coming to transplantation. **Conclusions:** These data suggest that lung transplant recipients with pulmonary hypertension have similar outcomes after single- or double-lung transplantation. These results support cautious preferential application of single-lung transplantation for pulmonary hypertension. (J Thorac Cardiovasc Surg 1998;115:397-403)

Lung transplantation is an established therapeutic option for patients with end-stage pulmonary vascular disease. We and others have been uncertain as to the best operation to offer individuals with severe pulmonary hypertension.¹⁻³ To compare outcomes after single- (SLT) and double-lung trans-

plantation (DLT) for pulmonary hypertension, we reviewed our experience at the University of Pittsburgh.

Patients and methods

Patient population. Between July 1989 and April 1996, 58 primary lung transplants were performed for pulmonary hypertension. Ages ranged from 14 to 61 years. Thirty-seven patients received DLT, and 21 patients underwent SLT. Pulmonary hypertension was defined as a mean pulmonary artery pressure greater than 30 mm Hg.⁴ All recipients were in New York Heart Association (NYHA) class III or IV before transplantation.

Donor selection and perioperative management. Donors were deemed acceptable on the basis of previously published criteria.⁵⁻⁷ Pulmonary preservation was carried out with Euro-Collins (EC) solution through April 1991 and thereafter with University of Wisconsin (UW) solution. Alprostadil (prostaglandin E₁; 500 μ g) was administered before infusion of preservation solution. Recipients

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Table I. Preoperative characteristics of patients undergoing SLT and DLT for pulmonary hypertension

Characteristic	SLT	DLT	p Value
Age (yr)	36	38	NS
Sex (M/F)	14:7	28:9	NS
Po ₂ (mm Hg)	70	62	NS
FEV ₁ (%pred)	85	77	NS
RVEF	25	31	NS
LVEF	59	64	NS
PAS (mm Hg)	93	105	NS
PAD (mm Hg)	40	50	NS
PAM (mm Hg)	61	70	NS
Diagnosis (primary/secondary)	6:15	13:24	NS
CI (L/min/m ²)	2.5	2.2	NS
TPG (mm Hg)	50	62	0.03
Donor Po/Fio ₂	467	460	NS

Po₂, Room air oxygen tension; FEV₁, forced expiratory volume in 1 second (liters); RVEF, right ventricular ejection fraction; LVEF, left ventricular ejection fraction; PAS, systolic pulmonary artery pressure; PAD, diastolic pulmonary artery pressure; PAM, mean pulmonary artery pressure; CI, cardiac index; TPG, transpulmonary gradient.

underwent standard pulmonary function testing before transplantation, as well as determination of left and right ventricular ejection fractions by radionuclide examination. Right heart catheterization data obtained in advance of transplantation were available for all recipients. Transpulmonary gradient was defined as mean pulmonary artery pressure minus pulmonary capillary wedge pressure. Donor characteristics were obtained from our procurement agency. Ischemic time was defined as the interval from donor crossclamping to reperfusion and for DLTs as the mean ischemic time for both grafts. Operative techniques were as previously described.⁸ Cardiopulmonary bypass was used in all cases.

Early and late allograft function and survival. Postoperative hemodynamics and gas exchange data (ratio of arterial oxygen tension to inspired oxygen fraction [Pao₂/Fio₂]) were examined for the first 24 hours. The diagnosis of diffuse alveolar damage was determined on the basis of histologic findings from autopsy or biopsy specimens. Duration of intubation, length of stay in the intensive care unit (ICU), and patient survival were recorded. Follow-up of 30-day survivors was 100% complete, with a mean 3.13 ± 0.41 years' follow-up in the SLT group and 3.24 ± 0.42 years' follow-up in the DLT group. The diagnosis of obliterative bronchiolitis was based on histologic criteria.⁹

Statistical analysis. Statistical computations were performed with JMP software (SAS Institute, Cary, N.C.). Comparisons between preoperative patient characteristics, postoperative Pao₂/Fio₂ ratios, pulmonary artery pressures, late spirometry values, length of ICU and hospital stays, and duration of intubation were done with the use of the unpaired *t* test. Actuarial survivals for the two groups were estimated by means of the Kaplan-Meier method and were compared with the Wilcoxon rank-sum test. Late functional status and the incidence of obliterative bronchiolitis were compared by means of the χ^2 likelihood ratio.

Table II. Operation performed by year

Year	SLT	DLT	% SLT
1989	0	2	0
1990	1	7	12.5
1991	8	8	50
1992	4	6	40
1993	2	7	22
1994	5	1	83
1995	0	3	0
1996	1	3	25

Results

Patient population: Preoperative characteristics and transplant procedure. Table I details the preoperative characteristics of the SLT and DLT groups. Systolic pulmonary artery pressures were markedly elevated in both SLT (93.1 ± 24 mm Hg) and DLT (105.3 ± 18 mm Hg) recipients (*p* = not significant). There was remarkable similarity between the two groups for all variables examined. Although there was a trend toward higher mean pulmonary artery pressures and lower cardiac indices in the DLT group, these differences did not reach statistical significance. The sole preoperative characteristic examined that differed between the two groups was the transpulmonary gradient, which was modestly higher in the DLT group (62 vs 50 mm Hg, *p* = 0.03). The frequency of SLT and DLT was evenly distributed throughout the years of the study (Table II). Among the 21 SLT recipients, 10 received right lung transplants and 11 received left lung grafts.

Donor characteristics were also well matched for both SLT and DLT groups. Pao₂/Fio₂ ratios were nearly identical, as was donor age (22.5 vs 28.5 years for SLT and DLT donors, respectively; *p* = 0.17).

Nineteen recipients had primary pulmonary hypertension, and 39 had secondary pulmonary hypertension. Twenty-nine of the secondary pulmonary hypertension group had Eisenmenger's syndrome as a result of an intracardiac defect; three patients had scleroderma, three had pulmonary thromboembolic disease, and one each had Osler-Weber-Rendu disease, pulmonary fibrosis, bronchopulmonary dysplasia, and pulmonary artery hypoplasia.

Duration of cardiopulmonary bypass and allograft ischemic times. As expected, ischemic and cardiopulmonary bypass times were longer in the DLT group (290 vs 333 minutes, *p* = 0.04; 151 vs 250 minutes, *p* = 0.0001).

Mortality. Actuarial survivals at 1 month were 81% and 84% for the SLT and DLT groups, respec-

Fig. 1. Actuarial survival of SLT and DLT recipients.

tively; survival was identical at 1 (67%) and 4 (57%) years (Fig. 1). Analysis of causes of death in the first year identified perioperative complications (bleeding, technical, and cardiac) and allograft dysfunction as the prime contributors to death during the first month. Infection (primarily pneumonia) was responsible for the majority of deaths during the remainder of the first posttransplant year (Table III).

Postimplantation hemodynamics and allograft function. Pulmonary artery pressures dropped immediately after allograft implantation and remained reduced for the first 24 hours. Mean pulmonary artery pressures were modestly higher in the SLT recipients 1, 12, and 24 hours after the operation (Fig. 2). P_{aO_2}/F_{iO_2} ratio was greater in the DLT group 1 hour after the operation but was not significantly different 12 and 24 hours after operation (Fig. 3).

Duration of mechanical ventilation and ICU and hospital length of stay. Excluding 10 patients surviving less than 30 days (6 DLT recipients and 4 SLT recipients), median duration of intubation (7.5 vs 10 days), ICU length of stay (10 vs 16 days), and hospital stay (32 vs 52 days) were not significantly different for the SLT and DLT groups, respectively.

Diffuse alveolar damage, rejection, and obliterative bronchiolitis. The incidence of histologically proven diffuse alveolar damage was similar for both groups: 43% for SLT and 51% for DLT recipients. Episodes of treated rejection in the first 100 days

Table III. Cause of death in the first year after transplantation

POD	SLT	POD	DLT
Day 0-30			
5	Unrecognized PFO/ graft failure	0	Intraoperative circula- tory collapse
15	Airway dehiscence	1	Intraoperative cardiac failure
19	Donor brain emboli, pneumonia	2	Allograft dysfunction
21	Graft failure	3	Operative bleeding
		15	Venous cerebral thrombosis
		24	Sepsis
Day 31-365			
39	Pneumonia	31	Graft failure (severe DAD)
101	PTLD	96	Pneumonia
225	Pneumonia	99	Pneumonia
104	Persistent rejection		
161	Pneumonia		
217	Pneumonia		

POD, Postoperative day; PFO, patent foramen ovale; DAD, diffuse alveolar damage; PTLD, posttransplantation lymphoproliferative disease.

(mean 2.8 episodes for SLT recipients and 2.9 episodes for DLT recipients) were also similar for both groups. Although the incidence of obliterative bronchiolitis was higher among SLT recipients (9/21, 42.9%), it was not significantly different from the incidence among DLT recipients (9/37, 24.3%, $p = 0.14$). Mean serum creatinine 1 year after transplan-

Fig. 2. Preoperative and postoperative mean pulmonary artery pressures (PA_{mean}) for SLT and DLT recipients. Results are expressed as mean $\pm$ standard error of the mean.

tation was 1.6 mg/dl for both SLT and DLT recipients.

Follow-up spirometry and functional status. Percent predicted forced expiratory volume in 1 second was similar for SLT and DLT recipients at up to 4 years after transplantation and was well preserved (Table IV). Review of functional status of current survivors demonstrated that more than 90% were in NYHA functional class I or II at the time of this report (Table V).

Status of patients with pulmonary hypertension on waiting list. During the period of this study, 58 patients with pulmonary hypertension died on our center's waiting list before coming to transplantation.

Discussion

This report describes an 8-year single-center experience with lung transplantation for recipients with pulmonary hypertension and contrasts the early and late-term results of patients receiving SLT and DLT. That the SLT and DLT groups were remarkably homogeneous in terms of preoperative characteristics reflects in part our uncertainty as to the better operation for these patients. Although this comparison is retrospective, comparison of outcomes between these groups is valid given their marked preoperative similarity (Table I). Although assignment to SLT or DLT was not randomized, this decision was often influenced by variables independent of the recipient, primarily donor organ availability.

Characteristics common to both SLT and DLT groups included a preponderance of women (42:16),

Fig. 3. Donor and postoperative P_{aO_2}/F_{iO_2} ratios for SLTs and DLTs. Results are expressed as mean $\pm$ standard error of the mean.

markedly depressed right ventricular function before transplantation, and preserved left ventricular function. Although preoperative pulmonary artery pressures were somewhat higher in the group undergoing DLT, there was substantial overlap and this difference did not achieve statistical (or clinical) significance. Application of SLT and DLT to patients with primary and secondary pulmonary hypertension was evenly distributed among the two groups. There was a trend toward a lower cardiac index in the DLT group (2.5 vs 2.2), although the difference was not statistically significant. Transpulmonary gradient was lower for the SLT than for the DLT group (50 vs 62 mm Hg, $p = 0.03$).

Implantation of one rather than two lungs carries the advantage of a shorter exposure to cardiopulmonary bypass and a shortened ischemic time. Mean ischemic time was 43 minutes less and duration of cardiopulmonary bypass 99 minutes less for SLT in this series.

An important measure of the quality of early graft function is the duration of mechanical ventilatory support, as well as length of stay in the ICU. The presence of two pulmonary allografts did not confer additional benefit based on these measures of outcome. We in fact found that median duration of intubation and ICU length of stay were somewhat shorter in the SLT group.

Although others¹⁰ have reported a higher incidence of obliterative bronchiolitis in SLT recipients with pulmonary hypertension, we did not observe a significant difference between the two groups, although there was a trend toward more prevalent obliterative bronchiolitis in the SLT group. At present the sample sizes in the two groups are too

Table IV. FEV_1 for SLT and DLT recipients (% predicted, $\pm$ SEM)

Group	6 mo	1 yr	2 yr	3 yr	4 yr
SLT	87.7 $\pm$ 6.5	84.8 $\pm$ 6.4	85.5 $\pm$ 6.2	80.9 $\pm$ 7.5	69.2 $\pm$ 9.0
DLT	71.0 $\pm$ 5.0	71.8 $\pm$ 5.3	74.3 $\pm$ 4.9	78.7 $\pm$ 5.3	70.8 $\pm$ 7.0
<i>p</i> Value	0.05	0.13	0.17	0.81	0.89
N	38	35	29	24	16

FEV_1 , Forced expiratory volume in 1 second; SEM, standard error of the mean

small to detect a difference. It is possible that obliterative bronchiolitis is detected earlier in the SLT group as a result of a smaller volume of functioning pulmonary parenchyma and that, with further follow-up, this difference will become clear.

A proposed disadvantage of SLT for pulmonary hypertension has been the possibility of poorer long-term functional results with a smaller volume of functioning lung parenchyma. A recent report from the St. Louis group¹¹ comparing long-term functional outcome after SLT and DLT for emphysema found that DLT provides superior long-term functional outcome as assessed by spirometry and exercise tolerance, as well as a trend toward improved late survival, and attributed these findings to the presence of more functioning lung allograft parenchyma after the onset of obliterative bronchiolitis. In contrast, we found identical functional status in both SLT and DLT groups late after transplantation for pulmonary hypertension. Spirometry demonstrated relatively well-preserved pulmonary function that was similar for both SLT and DLT groups 4 years after transplantation.

As has been previously reported, hemodynamics after SLT for pulmonary hypertension are characterized by a rapid and sustained drop in pulmonary artery pressures, substantial improvement in right ventricular function, and a preponderance (>90%) of pulmonary blood flow to the allograft as a result of high pulmonary vascular resistance in the remaining native lung.^{2, 12} In contrast, blood flow is evenly distributed between the two grafts in DLT recipients. The larger vascular bed in the DLT group yielded only modestly lower pulmonary artery pressures after transplantation and had no effect on early oxygenation. Boujoukos and colleagues¹³ have compared early allograft function in SLT recipients with emphysema and pulmonary hypertension. They convincingly demonstrate that excessive allograft blood flow and pulmonary hypertension are *not* major contributors to early graft dysfunction. Our experience with SLT and DLT for pulmonary hypertension does not support an early functional advantage to transplanting two lungs based on sim-

Table V. Late functional status among currently surviving lung transplant recipients

	NYHA class			
	I	II	III	IV
SLT	5	4	1	0
DLT	10	10	2	0

ilar lengths of ventilator support and duration of support in the ICU.

Our data supporting the application of SLT to patients with pulmonary hypertension are remarkably similar to those of Pasque and colleagues,¹⁴ who reported the results of 34 SLTs for pulmonary hypertension. Their series documents a rapid normalization of pulmonary artery pressures after transplantation (mean pulmonary artery pressure 25 ± 5 mm Hg, postoperative day 1) that is maintained over the long term after transplantation (mean pulmonary artery pressure 21 ± 6 mm Hg 4 years after operation). Survival in their experience was similar to ours, with a 3-year survival of 61%. Pasque and coworkers¹⁴ also report excellent long-term functional status, with 91% of current survivors in NYHA class I or II, as we found in our cohort.

In contrast to the present report, others have reported poorer outcomes after SLT for pulmonary hypertension. Review of the International Society for Heart and Lung Transplantation (ISHLT) registry data suggests a marginally worse outcome for SLT as opposed to DLTs for patients with *primary* pulmonary hypertension. Thirty-month survival for DLT recipients ($n = 199$) was 60%, as opposed to 48.4% ($n = 195$) for SLT recipients.¹⁵ This is in contrast to our experience with patients having primary pulmonary hypertension: a 3-year survival of 70% for SLT ($n = 6$) and 56% ($n = 13$) for DLT. Similarly, Pasque and colleagues reported 68% survival for 24 patients with primary pulmonary hypertension receiving SLT. It is notable that the ISHLT registry data identifies equivalent numbers of SLTs and DLTs for primary pulmonary hypertension.

The reality of limited pulmonary donor availability is demonstrated by the deaths of 58 patients with

pulmonary hypertension cleared for transplantation and waiting on the list at our institution during the time period of this study. The data reported here document similar early and late outcomes for recipients with pulmonary hypertension receiving SLT or DLT. Before this review our program had become progressively more conservative relative to SLT for patients with pulmonary hypertension because the majority of other programs have been more accepting of a DLT-only philosophy and admittedly these patients require more physician management early after transplantation. Currently we readily accept single lungs for those with modest and even supra-systemic pulmonary pressures. So long as left ventricular function is reasonable, we believe that SLT will immediately reduce pulmonary pressures to a degree that preoperative right heart dysfunction will not preclude success. Although we encourage cautious application of SLT for recipients with pulmonary hypertension, we believe that certain circumstances mandate DLT. We will avoid SLT if the donor is undersized relative to the recipient or if the donor lung is less than pristine. Given the opportunity to nearly double the supply of donor lungs, we believe that the operation of choice for recipients with primary or secondary pulmonary hypertension is SLT.

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Discussion

Dr. Bruce Reitz (Stanford, Calif.). My bias has been that for pulmonary hypertension, a DLT was a better option than an SLT, although the bias is built on a relatively small experience at Stanford in the late 1980s and early 1990s, many of these patients being operated on by Dr. Vaughn Starnes. It seemed to us that the mortality was similar, but in the period from 1 to 3 years, the effects of obliterative bronchiolitis were more prominent in the DLT group; perhaps they had less reserve once obliterative bronchiolitis became apparent. That does not seem to be the case with your data, so I guess we need to rethink our bias.

I have several questions: Six patients underwent lung transplantation for pulmonary hypertension in the more recent years of your series, 1995 and 1996. Five of the six had DLT and the other patient had SLT. Are the conclusions of your paper now changing your philosophy? Are you now offering *only* SLTs to these patients?

Dr. Gammie. The distribution of SLTs and DLTs throughout the years of our study was more or less even. The last 2 years reflects donor lung availability. Given the results of this study, however, we are shifting our emphasis toward SLT, and that is our operation of choice. There are a few instances in which we would not perform an SLT, specifically if we have an undersized donor lung or a marginal donor lung. We require a pristine lung of adequate size.

Dr. Reitz. Does the age of the recipient play any role in determining whether you would do a DLT or an SLT? For example, we believe that a DLT with more pulmonary tissue has a better functional capacity, and so we have tended to recommend DLT for younger recipients. Would that come into your thinking in pulmonary hypertension, or would you still advocate SLT even for a young patient?

Dr. Gammie. That has been the bias of some of the surgeons at our institution, but our data really do not support that conclusion. The average age of patients in the SLT group was 36 years and in the DLT group 38 years, so there was no difference in age between the two popula-

tions. On the basis of the measurements that we have done, there is no difference in long-term survival or functional status. Although that had been an underlying bias, I think that an SLT is preferable for any age group. We have to remember that we are able to serve two patients instead of just one patient by doing an SLT operation.

Dr. Reitz. I agree with you. However, the trend from the Registry seems to indicate that more and more DLTs are being performed while the number of SLTs remains the same or decreases. Your data indicating the efficacy of SLT are encouraging, but in practice many people do not seem to accept that.

My final question concerns the management of these patients. It had seemed to us that management of patients was more difficult after SLT. In your data, the results were the reverse: the SLT group spent less time on the ventilator and had shorter ICU stays. What made management of the DLT group more difficult? Was it simply the longer operation, the longer ischemic time, or was there no specific cause?

Dr. Gammie. Patients undergoing SLT will be kept sedated for the first 24 to 48 hours after the operation. Your are right. They do tend to be quite labile. The information that I presented was time on the ventilator, and we really did not find much of a difference. The disadvantages of DLT are precisely those that you mentioned: the longer time in the operating room and the longer time on cardiopulmonary bypass. They had almost twice as long a time on bypass, and I think that definitely influences their postoperative course. SLT is a quick operation, and it removes the primary modes of death of these patients—the most common cause of death being progressive right ventricular failure and the second most common cause, sudden cardiac death. When we perform an SLT, we remove this specter of death, and we really see no late deaths from these causes. Instead, they are replaced with the standard causes of death after lung transplantation—infection and rejection.

Dr. David M. Follette (*Sacramento, Calif.*). I have one question. Investigators at the University of Pennsylvania and other institutions seem to have found that the degree of pulmonary hypertension relative to the systemic blood pressure is important. Patients with supersystemic pulmonary artery pressures tend to have a much greater risk with SLT, and these investigators have moved to DLT in that group with much improved results. Have you compared the systemic to the pulmonary artery pressure, and have you seen any difference in your survival with those particular patients?

Dr. Gammie. I am aware of their bias. We did not

specifically look at that issue, although we looked at the pulmonary artery pressure, which was not different in the two groups and approached systemic pressure. We also looked at systemic blood pressure and found no significant difference in the two groups. I believe that we would not see a difference.

Dr. Douglas E. Wood (*Seattle, Wash.*). Despite your data showing no significant difference in the preoperative characteristics, if one looks at that list, there is a difference, albeit not significant statistically, in virtually every category. When you take that as a total, I wonder whether patient selection actually created more of a bias in your study than you would like to think. I actually agree with your result; it is our own bias as well to do SLTs as much as possible for pulmonary hypertension, both primary and secondary, but I would be cautious about your conclusions. Do you think that this would be a good project to study in a prospective fashion in a multiinstitutional basis, perhaps under the aegis of the Lung Transplant Study Group?

Dr. Gammie. That is an excellent suggestion. This was not a prospective randomized trial, and there were some trends, albeit insignificant, in selection of these patients. I stand by the data and I think that your suggestion of looking at this in a prospective fashion would not be unreasonable.

Dr. Paul F. Waters (*Los Angeles, Calif.*). I have a couple of questions. I am concerned that the conclusion is a little too strong. As someone who does both these operations, I do not think they are the same operation. The management of these patients differs, being more difficult with SLT recipients. How are these patients managed in the postoperative period? Did all or some of them get nitric oxide? Did they all need it? Did they all get alprostadil (prostaglandin E₁)? Was there any difference in the way they were managed and, subsequently, the outcome?

Second, if I understand you correctly, you use whatever is available. If a single lung is available, you perform SLT. If two lungs are available, you do DLT. Is that correct or is there any other processing involved?

Dr. Gammie. I agree with you. The SLT recipients do tend to have a rockier course in the first 24 to 48 hours after transplantation. We have not used nitric oxide routinely nor do we give alprostadil to all patients, but rather on an as-needed basis. Until recently, the decision to perform an SLT or a DLT was influenced both by the selection committee, which applied biases, as well as organ donor availability. We currently preferentially do SLTs for patients with pulmonary hypertension, provided that we have a good quality lung of adequate size.