Repair of congenital heart lesions combined with lung transplantation for the treatment of severe pulmonary hypertension: A 13-year experience

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Objective: In patients with severe pulmonary hypertension associated with congenital heart disease, we prefer to perform repair of the congenital heart disease and lung transplantation whenever feasible so as to augment the donor pool and avoid the cardiac complications associated with heart transplantation. We report our experience with repair of congenital heart disease and lung transplantation and compare the results with those of patients who underwent heart-lung transplantation during the same period.

Methods: The records of patients who had repair of congenital heart disease and lung transplantation (n = 35) and heart-lung transplantation (n = 16) between 1990 and 2003 were reviewed.

Results: The underlying congenital heart disease in the repair of congenital heart disease and lung transplantation group included transposition of great vessels (n = 2), atrioventricular canal defect (n = 2), ventricular septal defect (n = 9), pulmonary venous obstruction (n = 7), scimitar syndrome (n = 2), pulmonary arterial atresia or stenosis (n = 5), and others (n = 8). Thirteen of the patients undergoing repair of congenital heart disease and lung transplantation (37.1%) had the congenital heart disease repaired before lung transplantation; the remaining congenital heart disease repairs were performed concurrently with transplantation. Sixteen patients underwent heart-lung transplantation because of poor left ventricular function or single-ventricle anatomy. Freedoms from bronchiolitis obliterans at 1, 3, and 5 years were 72.9%, 54.7%, and 54.7% for the repair of congenital heart disease and lung transplantation group and 77.8%, 51.9%, and 38.9% for the heart-lung transplantation group, respectively. Survivals at 1, 3, and 5 years were 62.9%, 51.4%, and 51.4% for the repair of congenital heart disease and lung transplantation group and 66.5%, 66.5%, and 60% for the heart-lung transplantation group, respectively.

Conclusion: Repair of congenital heart disease and lung transplantation is a feasible treatment option. Long-term outcome is determined by associated complications related to lung transplantation. Despite the complexity of combined congenital heart disease repair with lung transplantation and the resulting perioperative morbidity, the patients had similar outcomes to those of patients who underwent heart-lung transplantation.

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Treatment options for patients with severe pulmonary hypertension associated with congenital heart disease (CHD) include a combined repair of the underlying congenital heart lesion and lung transplantation (CCLT) or heart-lung transplantation (HLT).

In patients with a correctable congenital cardiac lesion, we prefer to perform CCLT to preserve the native heart, avoid the long waiting times for heart-lung grafts, and avoid the cardiac complications associated with heart transplantation. We report our experience with CCLT and compare the results with those of patients who underwent HLT at this center during the same period.

Methods

Patients

Between July 1990 and September 2003, a total of 274 pediatric lung transplantation procedures were performed at St Louis Children's Hospital. During this time, 35 children underwent CCLT and 16 children underwent HLT. These two groups of patients form the basis of this report (Table 1).

Pretransplantation Diagnosis

Patients in the CCLT group had a heterogeneous group of correctable congenital lesions (Table 2). The diagnoses can be divided into four categories. The first category included patients with types of CHD known to lead to the early development of pulmonary hypertension. These included congenital pulmonary venous stenosis, scimitar syndrome, and uncorrected ventricular septal defect. The second category included patients who acquired pulmonary hypertension at an earlier date than would be expected on the basis of the CHD. An example from this group is onset of pulmonary hypertension in patients with an atrial septal defect. Children in the third category had pulmonary hypertension despite early and adequate correction of CHD (atrial septal defect or ventricular septal defect). The fourth category of patients had pulmonary hypertension in association with a functionally inadequate vascular bed. These lesions included tetralogy of Fallot, multiple peripheral pulmonary arterial stenosis, and pulmonary arteriovenous malformations. The HLT group included patients with pulmonary hypertension who also had congenital cardiac lesions that were considered uncorrectable, either on the basis of the underlying anatomy (eg, single-ventricle anatomy or physiology) or because of unsuccessful attempts at correction, patients unlikely to have a successful repair of the lesion, and patients with severely depressed left ventricular function (Table 2).

Pretransplantation Evaluation

All other organ systems were evaluated to assess viability before listing for transplantation. Patients were excluded from listing if there was evidence of serious irreversible organ injury. In addition, social circumstances were carefully investigated including a frank discussion with the parents regarding commitment and risks involved in the therapy. Mechanical ventilation or extracorporeal membrane oxygenation (ECMO) support were not considered absolute contraindications to transplantation. A major issue pertaining to the consideration for lung transplantation was whether there

was a reasonable chance of reversibility of the pulmonary hypertension. In some cases, patients were treated with prolonged courses of epoprostenol and/or inotropic agents. Lung transplantation was undertaken only when we were certain that the pulmonary hypertension was irreversible.

Transplant Technique

The bilateral sequential lung transplantation and HLT procedures were performed with techniques previously described.^{1,2} The approach was through a bilateral anterolateral transsternal (clamshell) thoracotomy incision for patients undergoing bilateral lung transplantation, an anterolateral thoracotomy that extended across the sternum into the contralateral chest for those undergoing single-lung transplantation, and a median sternotomy for those undergoing HLT.³ Cardiopulmonary bypass was used in all instances. In the CCLT group, bilateral sequential lung transplant technique was used in 30 patients, and single-whole lung transplantation was performed in 5 patients. When a cardiac lesion was to be repaired, this was done after bilateral recipient pneumectomy with the heart arrested. This provided a completely bloodless field to allow rapid repair of the intracardiac lesion.

Immunosuppression

"Triple drug" (cyclosporine [INN: ciclosporin], azathioprine, and steroids) immunosuppression was used. For the first posttransplantation year, the target trough cyclosporine blood level was 300 to 350 ng/mL; subsequent trough target levels were 200 to 300 ng/mL. The initial steroid dose was 0.5 mg/kg daily for prednisone. The steroid dose was progressively tapered with time to as low as 0.1 mg/kg every other day, but we do not believe it is appropriate to stop this drug entirely. An azathioprine dose of 1 to 2 mg/kg daily was administered as long as the patient's white blood cell count exceeded 3500 cells/mm³. All patients received prophylaxis against *Pneumocystis carinii* pneumonia either as sulfamethoxazole and trimethoprim three times per week (orally) or as monthly treatment with aerosolized pentamidine when sulfa allergy or intolerance was present. Prophylaxis against mucocutaneous candidal infections was also given. Patients at risk for cytomegalovirus infection received ganciclovir prophylaxis.

Posttransplantation Surveillance

Surveillance after lung transplantation was performed with frequent spirometry and serial bronchoscopy with biopsy and bronchoalveolar lavage. Bronchoscopy was performed at regular intervals after transplantation: at 2 weeks, 1 month, 2 months, and 3 months, and then every 3 months thereafter. Transbronchial biopsy was performed at these intervals and at any time there was a change in clinical status for which rejection was a plausible explanation. The technique of transbronchial biopsy performed in infants has been described.^{4,5} When tissue sampling was inadequate, and a change in clinical status persisted, open lung biopsy was performed. Full pulmonary function measurements were performed at the same intervals as for bronchoscopy. Children younger than 5 years are generally not able to fully cooperate for standard pulmonary function tests. They were therefore evaluated with infant pulmonary function tests performed with standard techniques.^{6,7} The diagnosis of bronchiolitis obliterans is more difficult in small infants because they are not able to perform

TABLE 1. Demographic characteristics and pretransplantation evaluation

	CCLT (n = 35)	HLT (n = 16)	P value
Age at transplantation (y, median and interquartile range)	1.7 (0.7-11.4)	14.8 (11.8-17.0)	<.001
Sex (No. female)	18 (51.4%)	10 (62.5%)	.384
Hemodynamic values			
Mean pulmonary arterial pressure (mm Hg, mean $\pm$ SD)	66.2 $\pm$ 10.6	68.4 $\pm$ 18.7	.621
Cardiac index (L/[min $\cdot$ m ²], mean $\pm$ SD)	2.4 $\pm$ 0.6	2.3 $\pm$ 0.8	.499
Pulmonary vascular resistance (Wood units, mean $\pm$ SD)	21.2 $\pm$ 6.8	30.1 $\pm$ 11.2	.008
Requirement of ECMO support at transplantation (No.)	4 (11.4%)	1 (6.3%)	>.999
Requirement of mechanical ventilation at transplantation (No.)	11 (31.4%)	1 (6.3%)	.075
Time on waiting list (d, mean $\pm$ SD)	150.2 $\pm$ 290.6	453.3 $\pm$ 402.5	.013

standard pulmonary function tests and thus cannot be assessed for bronchiolitis obliterans syndrome as defined by Cooper and colleagues.⁸ We used information from infant pulmonary function tests to assess for a fall of 50% in the ratio of specific flow at functional reserve capacity to functional reserve capacity per kilogram in the absence of other pathologic processes as a diagnosis of bronchiolitis obliterans.⁹ Open lung biopsy was undertaken to confirm or deny this diagnosis.

Statistics

Normally distributed continuous data are expressed as mean $\pm$ SD. Medians with ranges are used when continuous data are skewed. Categorical data are expressed as counts and proportions. Unrelated two-group comparisons were performed with paired, 2-tailed *t* tests for means of normally distributed continuous variables and the Wilcoxon rank sum test for skewed data. Fisher exact or χ^2 tests were used to analyze differences in proportions among the categorical data. Kaplan-Meier estimate was used to depict survival and freedom from obliterative bronchiolitis. Survival and bronchiolitis obliterans-free survival comparisons between groups of patients were completed with the Mantel-Haenszel log-rank test. All data analysis was performed with the SPSS software package (SPSS 11.0 for Windows; SPSS Inc, Chicago, Ill).

Results

Deaths on the Waiting List

Seventeen patients with pulmonary hypertension and CHD died while on the waiting list. Six of these were waiting for HLT, and the other 11 were to undergo CCLT. Five of the 11 awaiting CCLT were infants with pulmonary vein stenosis. The average time to death while awaiting lung transplantation in this group was 16 days, underscoring the critical nature of this diagnosis in the very young patients. Two other children with this diagnosis were seen later in life with unilateral pulmonary vein stenosis and died after 211 and 323 days on the waiting list. Although we generally view children with Eisenmenger syndrome with an unrepaired ventricular septal defect as being in relatively stable condition, 3 of the 11 children with this diagnosis died while awaiting CCLT. Excluding 1 patient listed for longer than 5 years, the average times from listing to death in the CCLT

TABLE 2. Diagnoses for transplantation

	No.
CCLT (n = 35)	
Ventricular septal defect	9
Pulmonary venous obstruction	7
Pulmonary artery atresia or stenosis	5
Atrioventricular canal defect	2
Transposition of great arteries	2
Scimitar syndrome	2
Others	8
HLT (n = 16)	
Single-ventricle anatomy or uncorrectable cardiac lesion	11
Severely depressed left ventricular function	5

and HLT groups were 162 and 125 days, respectively. The timing of referral would obviously have a major impact on these data.

Pretransplantation Data

The demographic and pretransplantation data of both CCLT and HLT groups are shown in Table 1. The underlying CHD diagnoses in both groups are shown in Table 2. The age distributions of patients in both groups are depicted in Figure 1. Pulmonary hypertension in both groups was managed with a combination of nitric oxide, epoprostenol, and inotropic agents. The difference in average age at transplantation between the two groups is related to those undergoing CCLT for pulmonary venous obstruction, primarily infants younger than 1 year. There was a significant difference in time on the waiting list for the two groups, with the CCLT group waiting approximately a third as long as the HLT group. This is a reflection of both difficulty in acquiring an adequate heart-lung block for those patients undergoing HLT and the younger age of those undergoing CCLT. More patients in the CCLT group were on life-support devices, a reflection of our reluctance to accept patients for HLT whose condition had deteriorated to the point of requiring mechanical ventilation or ECMO.

Figure 1. Age distributions for CCLT and HLT recipients.

TABLE 3. Outcomes after transplantation

	CCLT (n = 35)	HLT (n = 16)	P value
Early			
Requirement for posttransplantation ECMO support (No.)	5 (14.3%)	4 (25.0%)	.436
Reexploration for bleeding (No.)	16 (45.7%)	7 (43.8%)	.762
Coagulopathy (No.)	8 (22.9%)	3 (18.8%)	>.999
Vascular stenosis requiring dilatation or revision (No.)	5 (14.3%)	0	.248
Airway complication (No.)	6 (17.1%)	0	.159
Cardiac arrest (No.)	4 (11.4%)	1 (6.3%)	>.999
Duration of mechanical ventilation (d, median and IQR)	14 (3–33)	2 (2–6)	.007
Stay in pediatric intensive care unit (d, median and IQR)	18 (6–28)	5 (3–8)	.006
Hospital stay (d, median and IQR)	30 (15–47)	15 (10–19)	.010
In-hospital deaths (No.)	9 (25.7%)	5 (31.3%)	>.999
1990–1995	7/22 (32%)	4/8 (50%)	
1996–2003	2/13 (15%)	1/8 (13%)	
Late			
Diagnosis of post-transplant lymphoproliferative disease (No.)	5 (14.3%)	1 (6.3%)	>.999
Requirement for retransplantation (No.)	3 (8.6%)	2 (12.5%)	.643
Coronary artery disease (No.)	0	1 (6.3%)	>.999

IQR, Interquartile range.

Transplantation Data

Thirteen of the patients in the CCLT group (37.1%) underwent CHD repair before lung transplantation, whereas the remaining CHD repairs were performed concurrently with lung transplantation. Eleven patients in the HLT group underwent cardiothoracic procedures before HLT. In the CCLT group, 30 patients underwent bilateral sequential lung transplantation, and the remaining 5 had single whole-lung transplantation. The mean cardiopulmonary bypass times for CCLT and HLT groups were 187 ± 58 and 224 ± 127 minutes, respectively ($P = .161$).

Posttransplantation Data

The early and late outcomes after surgery are shown in Table 3. Three of the 5 patients who required ECMO support at the time of transplantation had successful weaning from ECMO and did not require further support after surgery. The remaining 2 patients, 1 each in the CCLT and HLT groups, required ongoing ECMO support after transplantation. Seven additional patients required ECMO support after transplantation, and these 9 patients were unable to be weaned from ECMO despite maximal medical therapy. All 9 patients (5 CCLT and 4 HLT) died in the

Figure 2. Kaplan-Meier survivals after transplantation stratified by CCLT and HLT.

Figure 3. Kaplan-Meier freedoms from bronchiolitis obliterans (BOS) after transplantation stratified by CCLT and HLT.

postoperative period. The posttransplantation care of these patients was generally quite complex. There was a high incidence of reexploration for bleeding in each group. Beyond that, the patients in the CCLT group were ventilated longer and stayed longer in the pediatric intensive care unit than those in the HLT group. Five of the patients in the CCLT group required stenting of either a pulmonary artery or pulmonary venous anastomotic stricture. There are no pulmonary vascular anastomoses in HLT, and this complication therefore did not occur in that group. Six of the patients in the CCLT group had airway strictures develop that required dilatation or stenting. None of the tracheal anastomoses in the HLT group developed complications.

Survival

Overall hospital survival for the CCLT group was 74%, and that for the HLT group was 69%. The causes of in-hospital deaths in the CCLT group were graft failure in 5 patients, severe intraoperative hemorrhage in 2 patients, and infection in 2 patients. Causes of 10 late deaths in the CCLT group were bronchiolitis obliterans in 3 patients, infection in 5 patients, and malignancy in 2 patients. Causes of 5 in-hospital deaths in the HLT group (31.3%) were graft failure in 2 patients, severe intraoperative hemorrhage in 2 patients, and infection in 1 patient. Causes of 2 late deaths in the HLT group were cardiac arrest related to coronary arteriopathy in 1 patient and infection in the other patient. The Kaplan-Meier survivals at 1, 3, and 5 years were 62.9%, 51.4%, and 51.4%, for the CCLT group and 66.5%, 66.5%, and 60% for the HLT group, respectively (Figure 2). There was an improvement in in-hospital mortality in the period of 1996 to 2003 relative to our earlier experience from 1990 to 1995 (Table 3). This was primarily related to better patient selection because we recognized the very high risk of bleeding in cyanotic patients who have had previous lateral thoracotomy incisions.

Late Complications

At a median follow-up of 2.7 years (interquartile range 54 days–7.1 years), 14 patients in the CCLT group and 6 patients in the HLT group had developed bronchiolitis obliterans. Kaplan-Meier freedoms from bronchiolitis obliterans at 1, 3, and 5 years were 72.9%, 54.7%, and 54.7% for the CCLT group and 77.8%, 51.9%, and 38.9% for the HLT group, respectively (Figure 3). There was no statistically significant difference between the two groups ($P = .442$). Other late outcomes are shown in Table 3. The cardiac repair was successful in most cases, except for 3 patients. One patient had residual mild to moderate mitral regurgitation after a mitral valve repair that had remained stable on follow-up. Another patient was found to have a residual patent ductus arteriosus after surgical ligation, and this was successfully occluded with coils. Another patient developed moderate aortic regurgitation after an arterial switch operation for the treatment of transposition of great arteries. This patient died of a severe viral infection and septicemia. These postoperative cardiac repair complications were not directly responsible for any late deaths.

Discussion

CHD is currently the most common indication for lung transplantation in children younger than 1 year.¹⁰ Among pediatric lung transplants performed between January 1991 and June 2002, as registered with the International Society of Heart and Lung Transplantation (ISHLT), it accounted for 48.8% of the indications in children younger than 1 year, 11.6% of the indications in younger children aged 1 to 10 years, and 3% of the indications in children aged 11 to 17 years. We previously reported our early experience in the treatment of children with CHD and pulmonary hypertension.^{3,11} This report forms a comprehensive update of our experience and long-term follow-up.

The patients in this report had various types of CHD in association with pulmonary hypertension. Patients in the CCLT group can be divided into four clinical categories as

previously described. Patients in the HLT group had single-ventricle anatomy or physiology associated with pulmonary hypertension, an uncorrectable cardiac lesion associated with pulmonary hypertension, or poor left ventricular function associated with pulmonary hypertension. In some patients, the relationship between the CHD and the development of secondary pulmonary hypertension was expected, such as in patients with a large, uncorrected ventricular septal defect. On the other hand, other patients had associated pulmonary hypertension without an obvious cause, such as patients with a functionally inadequate pulmonary vascular bed. These patients may have had pulmonary hypertension similar to primary pulmonary hypertension. Children with pulmonary hypertension in association with CHD therefore comprise a heterogeneous group of patients.^{12,13}

The initial approach to patients with CHD and pulmonary hypertension was HLT.¹⁴ Repair of congenital cardiac lesion and lung transplantation was first reported by Fremes and associates¹⁵ in 1990. Subsequently, other cases were reported in the literature.¹⁶⁻¹⁸ Our practice has been to perform repair of congenital cardiac lesion if the lesion is correctable with relatively straightforward standard techniques. One must recognize that a complex repair requiring prolonged myocardial ischemia will result in elevation of the left ventricular end-diastolic pressure and subject the newly transplanted lungs to pulmonary edema. Thus we would caution against any procedure resulting in myocardial ischemic times in excess of 60 minutes.

The patients in the CCLT group were clearly different from those in the HLT group in that the former group consisted of patients who had correctable congenital cardiac lesions. Treatment was tailored to repair the congenital lesion and perform lung transplantation for the treatment of pulmonary hypertension. In contrast, HLT was in general reserved for patients with pulmonary vascular disease in association with an uncorrectable congenital cardiac lesion, single-ventricle anatomy or physiology, or severely depressed left ventricular function. Although we have compared the two groups, they include quite different patients, even given the common theme of CHD and pulmonary hypertension. We approach all patients with this combination initially looking at the feasibility of lung transplantation alone with repair of the cardiac lesion. Only those not deemed appropriate for that approach are listed for HLT.

There are several advantages of CCLT relative to HLT. These include preservation of the native heart, shorter waiting time for donor lungs than for a heart-lung block, augmentation of the donor pool by allowing the another donor heart to be placed for a potential cardiac recipient, and avoidance of complications associated with cardiac transplantation. HLT has the advantages of replacing a structurally abnormal heart with a normal heart and the relative

simplicity of the operation itself. HLT has the disadvantages of complications associated with cardiac transplantation, as seen in a patient in the HLT group who died of transplant coronary vasculopathy. Although the number of patients in the pediatric registry is too small to analyze, in the adult population of patients undergoing HLT, transplant coronary vasculopathy accounts for 5% to 10% of all late deaths. Approximately 1 in 6 organ donors has lungs suitable for donation. Thus not every potential cardiac donor will have suitable lungs for transplantation. Donor hearts are allocated to status 1A heart transplant recipients, ahead of patients awaiting heart-lung blocks. The average waiting time for donor lungs in the CCLT group was 150 days, whereas there was a markedly longer waiting time (average of 453 days) for HLT blocks. The overall survival of children undergoing HLT has been worse than that of those undergoing lung transplantation alone, as noted in the Registry for the ISHLT.¹⁰ Perhaps in view of these reasons, the number of pediatric HLTs performed as registered with the ISHLT has continued to decrease through 2001, and the overall number performed worldwide in 2001 was approximately 10. The ISHLT registry showed that the number of infant and child HLT recipients has decreased to negligible numbers, and even the number of adolescent recipients has decreased with time.¹⁰

Right single-lung transplantation was performed in 3 of the 5 patients in our initial experience.³ Early reports had suggested that single-lung transplantation might be applicable to the very young patient, with satisfactory relief of pulmonary hypertension and maintenance of good cardiac function.¹⁹ Bilateral lung transplantation, however, has been our preferred technique since 1993. We have preferred bilateral lung transplantation because we hope that it will provide the maximum possible pulmonary vascular bed and alveolar volume for continued lung growth and development.^{3,9,20} The ISHLT data have shown that bilateral lung transplantation is associated with an improved survival after single-lung transplants for pediatric recipients.¹⁰ In the CCLT group, 5 patients underwent single-lung transplantation early in our program, whereas the remainder underwent bilateral lung transplantation.

The patients in the CCLT group were younger and appeared to be a sicker cohort of patients, with about a third requiring preoperative mechanical ventilation and 11.4% requiring ECMO support. Their postoperative course was also more complicated, with a longer stay in the intensive care unit and a longer overall hospital stay than in the HLT group. After transplantation, however, the two groups of patients had similar in-hospital mortalities, with primary lung graft failure as the predominant cause of death. Among the hospital survivors, patients from the CCLT and HLT groups had similar freedoms from bronchiolitis obliterans and survival. None of the patients in the CCLT group died

in the long term as a result of complications directly related to the repaired congenital cardiac lesion. After transplantation, we observed that most morbidity and mortality was related to complications of transplantation, such as primary donor lung graft failure, infection, neoplasms, and bronchiolitis obliterans. It is seen that repair of congenital lesion in the CCLT group was feasible and did not cause any long term morbidity or mortality. The survival after hospital discharge and incidence of bronchiolitis obliterans were similar to a group of patients undergoing lung transplantation at St Louis Children's Hospital for other indications. The ISHLT results have also shown that the causes of death after pediatric HLT are comparable to those seen after lung transplantation, with graft failure accounting for 50% of deaths within 30 days; after 1 year, bronchiolitis obliterans accounted for approximately 50% of deaths.¹⁰

The in-hospital mortality dropped significantly in both groups in a later era relative to our early experience. That is most likely attributable to better candidate selection. We recognized early on that the adhesions after thoracotomies in patients with cyanosis and pulmonary hypertension were extraordinarily vascular and dense. These adhesions are quite different from those observed in patients with cystic fibrosis who have had previous thoracotomies. Arterial collateral vessels arising from the intercostals, internal thoracic, and axillary arteries penetrate into the lung parenchyma to provide more pulmonary blood flow. These vessels become large and are quite difficult to control during the recipient pneumonectomies. This results in considerable blood loss, longer time on cardiopulmonary bypass, post-transplantation reexploration, hemodynamic instability, and transfusion with multiple blood products. All contribute to the risk of early graft dysfunction.

In summary, this article reviews our experience with two treatment strategies available for the treatment of a heterogeneous group of patients with CHD. CCLT was used for patients with correctable congenital cardiac lesions, whereas HLT was used when the CHD lesion was not amenable to repair. Both CCLT and HLT are feasible surgical treatment strategies, and the in-hospital mortalities have markedly improved with time. Despite the complexity of performing a combined congenital cardiac lesion repair with lung transplantation and the resulting increased perioperative morbidity, the patients had an in-hospital mortality and long-term outcomes similar to those of patients who underwent HLT. Early and long-term outcomes were determined by associated complications related to lung transplantation. We conclude that for patients who require lung transplantation for pulmonary hypertension associated with CHD, correction of the cardiac lesion should be undertaken when possible to avoid the potential disadvantages and complications associated with HLT.

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Discussion

Dr Vaughn A. Starnes (Los Angeles, Calif). This report reviews the outcomes of 51 infants, children, and adolescents treated for CHD and pulmonary hypertension. Thirty-five children were

treated with CCLT, and 16 children were treated with HLT. I might add that this experience was extracted from a very large pediatric lung transplantation experience of more than 274 patients. So this group has selected a very demanding population of patients. As clearly outlined in the article, HLT is becoming, or already has become, a treatment option that is not available because of the limited donor pool. Therefore this experience with CCLT is increasingly important for this group of children with Eisenmenger physiology. I have several questions, Dr Huddleston. Which congenital heart defects were repaired before transplantation, and why? You report that about 20% of these patients had some kind of previous repair. Was that a palliative repair that led to repair of the heart defect, and then transplantation?

Dr Huddleston. This was a very complicated group of patients because of a variety of diagnoses and treatment. Among the CCLT group of patients who had a previous repair, half of those patients had a palliative operation while the other half had a corrective operation of the congenital heart defect. The 2 patients with transposition of the great arteries who underwent transplantation had undergone an arterial switch during infancy, at an appropriate time, within the first week after birth, but had persistent and progressive pulmonary hypertension, and went on to transplantation because of that.

Dr Starnes. There was a large group of these children with airway or vascular complications. I would assume that those were in the younger age group. If so, are there any technical points that you can share with us that might improve the outcome? You had a very large group of infants with pulmonary vein stenosis. Is there anything that you can impart to us, such as absorbable sutures, running suture lines, or anything that you could tell us?

Dr Huddleston. We use absorbable suture for all the anastomoses in the first place. The airway problems were distributed throughout the age groups. They were not concentrated in the infants. As for the pulmonary vascular anastomotic complications, arterial stenoses occurred only in the left pulmonary artery. I think the reason, at least in part, is that the left pulmonary artery in these patients is oriented in a more posterior direction than in a normal setting. I don't have a good explanation for that, but in the patients who had left pulmonary artery stenosis or near occlusion after transplantation, the angiograms show this somewhat oblique take-off at the anastomosis from the native pulmonary artery. So what we started to do to counteract that was to take the anastomosis almost to the main pulmonary artery and not put it out further onto the left pulmonary artery. So that would be my suggestion, and is what we've done to try to avoid the arterial anastomotic problem.

Dr Starnes. Just one further technical issue. In these small children, the phrenic nerve is close to pulmonary venous cuffs. And I noticed that there was a lengthy time on the ventilator for some of these children. Was that related to phrenic nerve injury, or was it just a graft issue?

Dr Huddleston. In this case it was almost all graft issues. No phrenic nerve issues kept these children on the ventilator.

Dr Starnes. With a limited donor pool of pediatric lungs, we need to decide on the best recipient. Do we put the lung in a child with a congenital heart lesion that we're going to repair, or do we put it into another child? On the basis of your experience, do you have any thoughts about that? Are there some patients who should not undergo this therapy?

Dr Huddleston. I believe that patients who have had previous thoracotomies probably should not undergo transplantation in this setting. The collateral vessels that develop in this situation, as I'm sure all of you know, can be enormous, and can produce formidable bleeding during lysis of adhesions. A previous sternotomy would not preclude transplantation, but certainly a previous thoracotomy incision should be an absolute contraindication.

Dr Thomas L. Spray (Philadelphia, Pa). This is a nice summary of a long experience. I have a couple of brief questions.

What you've shown here is that there are two groups of patients, one young relative to the other, and yet the incidences of bronchiolitis obliterans were similar out to the length of follow-up. Like the report from the larger experience at Washington University presented at this meeting a couple of days ago, there was no real difference in the incidence of bronchiolitis obliterans, and yet one was a relatively young patient population (a mean age of 1.5 years) and the other was a relatively older population (mean age of 14.7 years).

Some previous reports have suggested that the younger patients have a relatively more beneficial course in terms of bronchiolitis obliterans. Are you backing away from that? Do you believe that that's really the case, that younger patients have a preferential immune status in lung transplantation as they do in heart transplantation, or do you think that this ongoing experience now is evening out some of that observed difference?

Dr Huddleston. That's a good question. The real advantage, immunologically, that we've seen in terms of looking at acute rejection in bronchiolitis obliterans has been in the even younger age group, that is, those 6 months old or younger. The group of patients undergoing transplantation in that age range have been primarily those with congenital lung diseases, rather than, say, pulmonary vein stenosis, which comprises a large portion of the infant population in this report. So no, we're not backing away from that notion, but pushing the age further toward the neonatal period to say whether the advantage immunologically arises.

Dr Spray. Second, you had two groups, one spanning about a 5-year period and the other spanning about an 8-year period. And in the second group, which was 1996 to 2003, the number of patients undergoing CCLT was lower than in the first group, which spanned a shorter period. You suggested that you've changed your selection criteria, and maybe that accounts for some of the difference. What kinds of changes have you made in your selection criteria? Has it just been in terms of thoracotomy and bleeding issues, or are there other more subtle changes in your selection criteria that account for the decrease in number more recently?

Dr Huddleston. It has been because we've really stayed away from the kids that have had previous thoracotomies. I think that's really been the main issue that we've addressed, trying to stay away from that patient population.

Dr Spray. Thoracotomy with or without cyanosis, or do you think it matters?

Dr Huddleston. Well, they virtually all have cyanosis.

Dr Spray. The patients with pulmonary vein stenosis have cyanosis?

Dr Huddleston. None of those have had previous thoracotomies, in general.

Dr Marshall L. Jacobs (Philadelphia, Pa). Dr Huddleston, compliments on managing this incredibly challenging group of

patients. You did show very clearly that there was considerable attrition while awaiting transplantation for both groups. Obviously, for the infants with pulmonary vein problems and so on, you have very little choice in terms of timing. After mentioning the waiting list deaths, you advised transplantation for these patients before they get too sick.

How would this experience affect your advice to cardiologists and families of adolescent patients who are exercise limited but in relatively stable condition with Eisenmenger physiology from cardiac lesions associated with left-to-right shunt? Is there an optimal time for referral, or does one wait until there is hemoptysis, arrhythmias, and morbid events?

Dr Huddleston. That's a good question. I think for the typical patient with Eisenmenger syndrome, such as a patient with a ventricular septal defect, these patients can live for a long time. Now, we did have some in our group that, for whatever reason, had progressive disease and required transplantation to avoid death. Most of those deaths were patients with more complicated disease than just that. Pulmonary vein stenosis actually made up a fairly large percentage. Single-ventricle anatomy, complicated single ventricles that had failed palliative operations (Glenn shunt, etc), were in that group as well.

So my focus would be on pulmonary vein stenosis or lesions in that area that are a problem. Historically, there's been some reluctance to go after the pulmonary veins primarily with some of the operations that the Toronto group has described. And when I get called about these kids now, I always encourage the referring center to do those operations, to approach it like that, because of this problem with deaths while on the waiting list.

Dr Jacobs. So in reality, given the fact that organs gets allocated to the most severely ill patients, is there really, at this time, limited application of this therapy to a patient with a ventricular

septal defect and Eisenmenger syndrome? Are those becoming a very small group?

Dr Huddleston. Well, organs aren't allocated according to severity of illness for lungs or heart-lung blocks. That's only for other organ transplant groups. So it's first come, first served for lungs.

Dr Jacobs. Well, the patient between the teens and the third decade of life, who is functionally limited but not morbidly ill with Eisenmenger syndrome from a ventricular septal defect or from untreated truncus arteriosus, are some of those patients included in this group? And at what time do you refer those patients for transplantation?

Dr Huddleston. Those patients come to transplantation when they have heart failure in conjunction with their cyanosis. We really try to tease out the ones who have a very limited survival, recognizing that it is difficult, and also, even with some heart failure you can live for a long, long time. So we try to identify those who are really at the end stage.

Dr Gary K. Lofland (*Kansas City, Mo*). I just want to congratulate you and your colleagues on a courageous undertaking and a beautiful presentation. I do have one technical question, which may be addressed in the article. Do you think that some of the difference in pretransplantation pulmonary vascular resistance between the two groups could be attributable to the difficulty inherent in accurately calculating pulmonary vascular resistance in a single-ventricle population? We encounter that in our Fontan population.

Dr Huddleston. I think that's probably right, in that it was very difficult to get at those numbers.

I would like to thank Dr Spray for his many contributions to the development of this program in the first place back in the early 1990s.