Lung and Heart–Lung Transplantation

Evolution and New Applications

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Heart–lung transplantation (HLT) and lung transplantation (LT) are effective treatment modalities for patients with advanced pulmonary parenchymal or vascular disease. Lung transplantation offers potential advantages over HLT, including reduced pretransplant waiting time and improved efficiency of organ utilization, and is currently being offered to patients formerly treated by HLT. To explore the relative merits of these procedures, the authors examined the results in 44 procedures (23 HLT and 21 LT) in 42 patients transplanted at their institution. Heart–lung transplant recipients included 20 adults and three children (ages 5, 5 and 3). Most HLT patients had primary pulmonary hypertension (PPH) (n = 9) or Eisenmenger's syndrome (ES) (n = 8). Twenty-two of twenty-three patients have been long-term survivors (mean follow-up = 17.8 months, Kaplan-Meier survival at 12 months = 85%). Obliterative bronchiolitis (OB) has occurred in five patients (22%), and all have died. Of 21 LTs in 19 patients, nine had obstructive and eight had restrictive lung diseases. Three single-LT (SLT) patients had PPH, and one had ES secondary to a ventricular septal defect. Mean pulmonary artery pressures fell from 55 ± 6 mm Hg before SLT to 21 ± 3 mm Hg after SLT; $p < 0.001$. Three pediatric patients (ages 4, 10, 17, and 17[re-transplant]) have undergone four SLTs. With mean follow-up of 6.4 months, LT patients have survival at 12 months of 80% (Kaplan-Meier). Lung transplant patients wait a far shorter time for their transplant than do HLT patients (166 *vs.* 384 days, $p < 0.03$). Three patients (19%) have evidence of OB after SLT, with one death. By virtue of equal intermediate-term outcomes, shorter waiting times, and better use of donor organs in comparison with HLT, LT should be offered whenever possible to patients with end-stage pulmonary parenchymal or vascular disease. The authors' pediatric LT and HLT experience (7 treatments in 6 patients) is the largest reported to date and demonstrates the utility of these procedures in this group. Chronic rejection (OB) remains the greatest impediment to long-term survival in both LT and HLT pts.

AFTER THE PIONEERING work of Reitz et al.,[1] who demonstrated the feasibility of transplanting pulmonary tissue with the first successful heart–lung allografts, and Cooper et al.,[2] who first successfully transplanted a single lung, recent years have witnessed a rapid evolution in the approach to the patient with end-stage lung disease. Primarily because of the severe limitation in available donor organs, many patients who formerly would have been offered heart–lung transplantation are now receiving lung transplants. In this report, we describe our experience with heart–lung and lung transplantation and offer our views regarding the relative merits of, and indications for, these two procedures.

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Materials and Methods

Recipient Selection

Only patients with end-stage pulmonary or cardiopulmonary disease are considered for transplantation. All patients are disabled and most require supplemental oxygen therapy. There must be no other medical or surgical options available that are deemed likely to afford any substantial benefit within a reasonable degree of medical certainty. All individuals selected are deemed to be experiencing the last 24 to 36 months of their natural lives. Patients are screened for the presence of other disorders that might have an impact on survival independent of their pulmonary or cardiopulmonary disease. Psychosocial suitability and compliance also are analyzed before placement on the waiting list.

Donor Selection

Donors in all cases were multiple-organ donors. Donor selection criteria are listed in Table 1. Size matching is relatively more important in cases of heart–lung or bilateral lung transplantation. In these cases it is imperative not to oversize the donor lungs. In single-lung transplants,

a greater disparity in size between donor and recipient may be tolerated. A lung from an individual either larger or smaller than the recipient may be accommodated because of the ability of the mediastinum to shift and the contralateral lung to expand or be compressed, such that space problems have not been prevalent despite large differences in lung volumes between donor and recipient. Pulmonary function must be well maintained. Arterial PaO_2 of 100 mm Hg or greater on a fraction of inspired oxygen (FIO_2) of 0.4 must be demonstrated. In addition lung compliance must be normal (peak airway pressure of no greater than 30 mm Hg with a normal tidal volume). The chest radiograph should be clear, and sampled pulmonary secretions should demonstrate no gram-negative or fungal organisms. Because of the potential occurrence of graft-*versus*-host disease in the form of hemolytic anemia with its attendant complications when ABO compatibility, but not identity, is observed, we currently require ABO identity between donor and recipient.

Operative Strategies

Heart–Lung Transplantation. All heart–lung transplantation (HLT) procedures are performed with cardiopulmonary bypass. Meticulous attention to posterior mediastinal homostasis must be observed. The heart is removed and the phrenic nerves are isolated on generous pedicles of pericardium. Subsequently the lungs are individually removed by dividing the inferior pulmonary ligaments and transecting the pulmonary hilar structures with a TA-90 surgical stapling device. This facilitates the removal of the lungs and improves hemostasis. Sufficient posterior left atrium is then removed to allow unimpeded passage of the donor right lung posterior to the right atrium and into the right pleural space. The donor heart–lung bloc then is placed into the recipient chest and the tracheal anastomosis is performed. Continuous polypropylene is employed in the adult, and interrupted polypropylene in the pediatric age group, to allow growth to occur at the anastomotic site. Donor and recipient aorta and right atrium then are anastomosed, completing the implant.

TABLE 1. *Donor Selection Criteria*

Criteria
Immunologic
ABO identical
Crossmatch required in sensitized patients
Pulmonary function
Chest radiograph clear
paO_2 100 mmHg or > on FiO_2 0.4
Lung complicance normal
Peak airway pressure 30 mmHg or less with normal tidal volume
Microbiologic
No obvious pulmonary sepsis
Pulmonary secretions
Absence of gram-negative or fungal organisms
Size match
Heart–lung or bilateral lung transplant
Donor lung volume same or less than recipient
Single lung transplant
Donor lung volume less critical
May be larger than recipient

ABO, ABO blood group system.

Lung Transplantation. Single-lung transplants (SLTs) are performed through an anterolateral thoracotomy, employing modifications of the technique described in animals by Metras in 1950[3] and by Hardin and Kittle in 1954.[4] Patients are intubated with a double-lumen endotracheal tube to allow the lung being replaced to be deflated. This allows the hilar structures to be mobilized and divided. We have found it advantageous to occlude the ipsilateral pulmonary artery with a tourniquet soon after entering the chest and deflating the lung. This maneuver prevents shunting of blood through an unventilated lung, and resultant hypoxemia. If the patient develops unacceptable levels of hypoxemia or hypercarbia, the lung can be reperfused and ventilated while cardiopulmonary bypass is instituted by the femoral approach or through the chest. All patients with pulmonary hypertension, either primary pulmonary hypertension (PPH) or Eisenmenger's syndrome (ES), who undergo SLT require the institution of cardiopulmonary bypass. Figures 1 through 3 depict the technique of SLT. In Figure 1, the diseased recipient lung has been removed. The bronchial anastomosis has been accomplished with interrupted nonabsorbable suture material. Vascular clamps are in position on the pulmonary artery and across the base of the pulmonary veins. Figure 2 shows the omental pedicle being wrapped around the bronchial anastomosis for protection, and to provide an exogenous blood supply. In Figure 3, the pulmonary artery anastomosis has been completed, and the anastomosis between donor and recipient left atrial cuffs is being accomplished. This anastomosis completes the implant procedure. The lung is flushed antegrade and retrograde with blood, and the clamps are released, restoring perfusion to the lung. When hemostasis at the pulmonary hilum is secure, ventilation of the graft can be initiated.

Bilateral Single-lung Transplantation. The technique of *en bloc* double-lung transplantation with tracheal and posterior left atrial anastomoses as reported by the Toronto group is of historic interest only because of the reported high incidence of airway complications attending its use.[5,6] This procedure has been modified by the Washington University group of Pasque et al.[7] to a method of bilateral SLTs with individual bronchial anastomoses. This procedure can be performed without the routine necessity of cardiopulmonary bypass in certain cases. With the double-lumen endotracheal tube and careful monitoring of arterial blood gases, it is possible to alternately

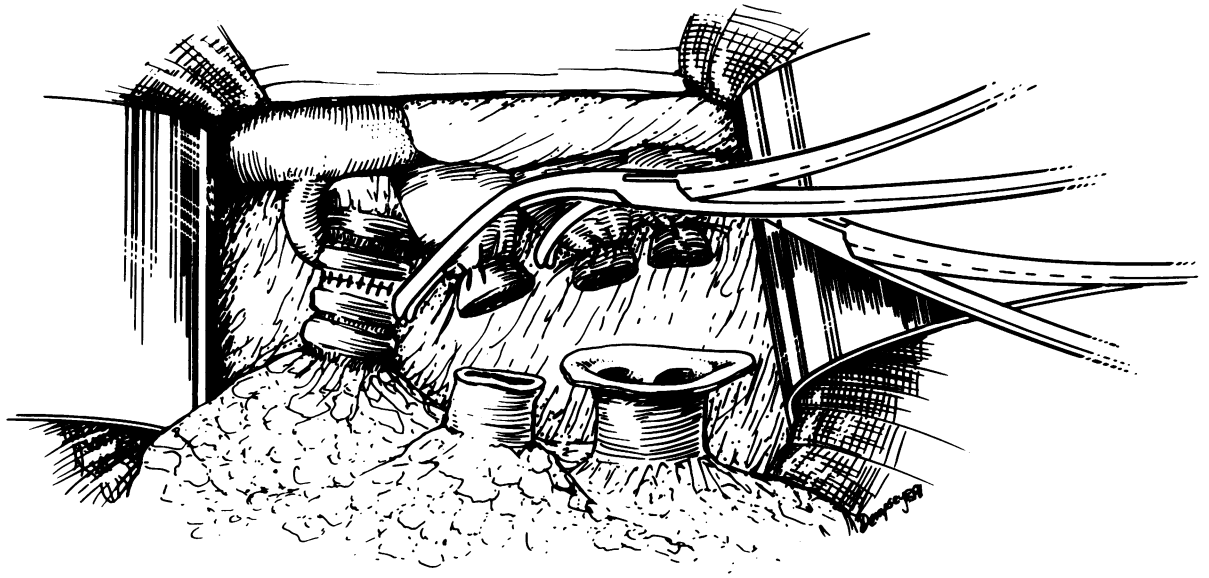

FIG. 1. Technique of right single lung transplant. Bronchial anastomosis has already been completed.

deflate the diseased lungs to mobilize the hilar structures. One allograft lung then can be implanted and the patient supported with this graft during implantation of the second, contralateral graft. This procedure is greatly facilitated by the use of the bilateral transverse thoracotomy, crossing the sternum at the level of the fourth intercostal space. The exposure is excellent, and the avoidance of bypass can greatly decrease operative hemorrhage.

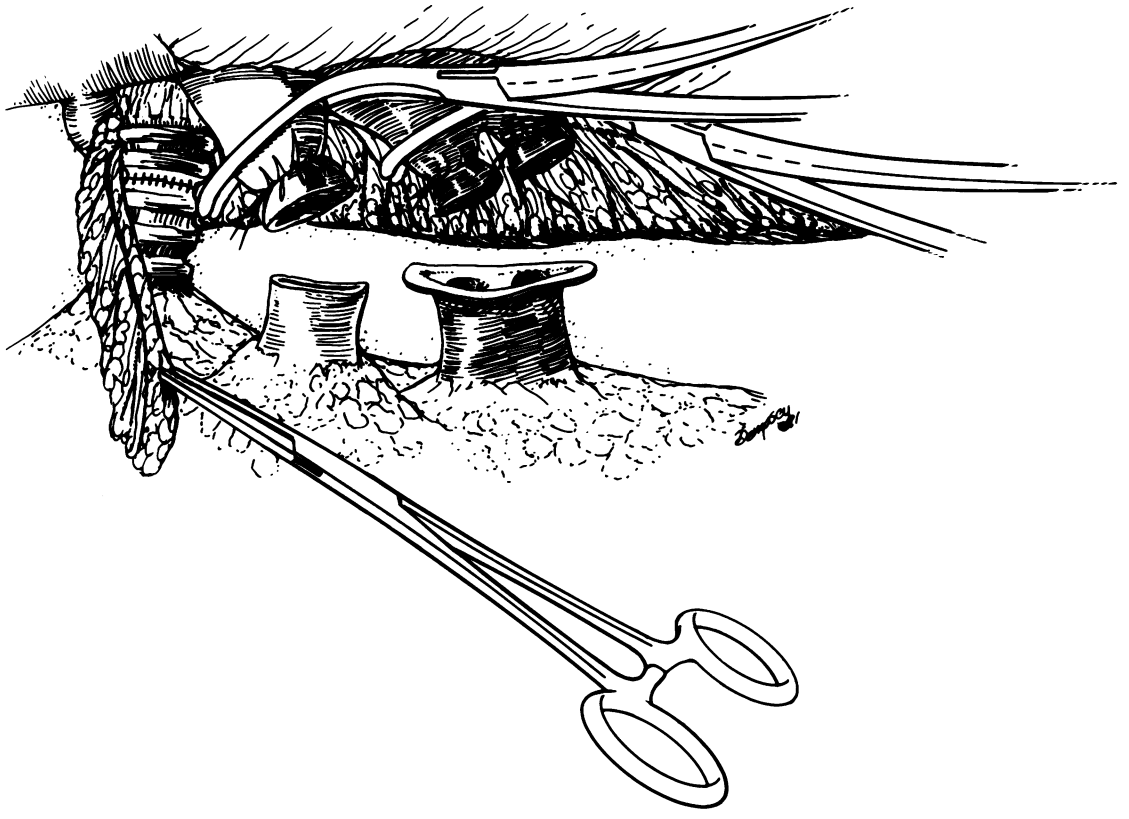

FIG. 2. Technique of single lung transplant. The omental pedicle graft is shown being wrapped around the bronchial anastomosis.

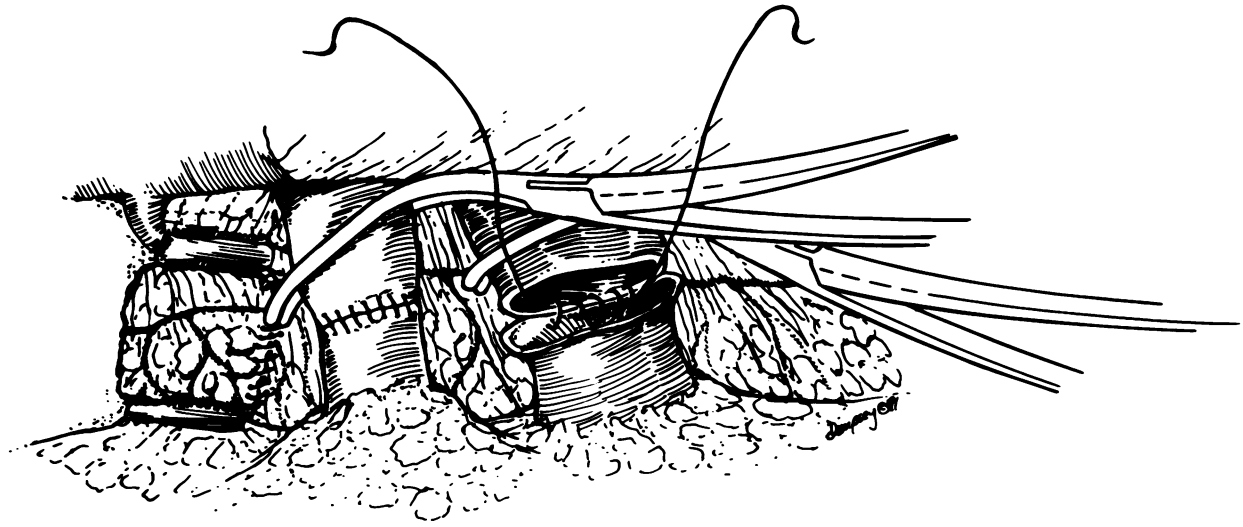

FIG. 3. Technique of single lung transplant. The completed pulmonary artery anastomosis is shown, and the left atrial anastomosis is being performed. This anastomosis completes the implant procedure.

Immunosuppression

All recipients receive immunosuppression according to the so-called "triple-therapy" protocol introduced at the University of Minnesota in 1983 for cardiac transplantation.[8] Table 2 outlines the details of this regimen. Cyclosporine (CSA) is initiated preoperatively in a small dose (4–8 mg/kg), depending on renal function. Postoperatively CSA is administered as a low-dose continuous infusion (2–3 mg/hr). In addition, CSA is administered orally in a dose of 4 to 6 mg/kg/day in two divided doses 12 hours apart. Azathioprine is administered preoperatively in a dose of 2 to 3 mg/kg and postoperatively is targeted to a white blood cell count of 4000 to 5000 cells/mm^3. Methylprednisolone is administered intraoperatively in a dose of 500 mg and postoperatively 125 mg every 8 hours for three doses. Steroids then are withheld for 10 to 14 days to promote healing of the airway anastomosis. At around day 10 to 14, prednisone is initiated at 0.5 mg/kg/day. A portion of the recipients have received antilymphocyte therapy in the form of Minnesota anti-lymphocyte globulin for 3 to 5 days after transplant. This allows the use of lower CSA doses in the interest of preserving optimal renal function during the critical first several days.

TABLE 2. *Immunosuppression for Lung, Heart-Lung Recipients*

Treatment
Preoperative
CSA 4–6 mg/kg orally depending on renal function
AZA 2–3 mg/kg orally
Intraoperative
MP 500 mg I.V. at time of reperfusion
Postoperative
CSA
Oral (NG) 2–4 mg/kg/day in two divided doses
I.V. 2–3 mg/hr as continuous infusion
AZA 2–3 mg/kg/day orally (NG)
Decrease for WBC < 5000/mm^3
MP 125 mg I.V. every 8 hours for three doses
Minnesota anti-lymphoblast globulin (MALG) 15 mg/kg I.V. every day for 3 to 5 days
Prednisone beginning day 10–14 0.5 mg/kg/day
Maintenance
CSA 5–6 mg/kg/day in two doses
AZA 1.5–2.5 mg/kg/day
Prednisone taper to 0.1 mg/kg/day by 3 to 6 months

CSA, cyclosporine; AZA, azathioprine; MP, methylprednisolone; NG, nasogastric.

Infection Prophylaxis

All patients receive perioperative vancomycin for the 24 hours surrounding surgery and cefamandol until all drainage catheters and monitoring lines are removed. Recipients who are cytomegalovirus (CMV) seronegative before transplant receive exclusively CMV-negative blood and blood products. All patients receive high-dose acyclovir (3200 mg/day) and mycostatin for 90 days after transplant, and trimethoprim-sulfamethoxazole indefinitely. Donor and recipient airways are cultured at the time of surgery to facilitate a more rational selection of antibiotic therapy in the early post-transplant period. Every attempt is made to treat only identified infections and to avoid the indiscriminate use of antibiotics, lest fungal or resistant bacterial overgrowth develop.

Postoperative Surveillance

Patients are assessed carefully for signs of infection and rejection in the post-transplant period. Fiberoptic bronchoscopy (FOB) is employed liberally in this effort. Bronchoalveolar lavage (BAL) has proven of great utility in

the diagnosis of infection and transbronchial biopsy (TBB) in the diagnosis and monitoring of rejection episodes. Fiberoptic bronchoscopy is performed generally within the first 24 hours of surgery to assess the airway anastomosis, and thereafter is indicated for any significant change in the patient's clinical status, chest radiograph, or arterial blood gases. Routine FOB with BAL and TBB is performed on a protocol basis every 7 to 10 days during the transplant hospitalization, and subsequently at gradually increasing intervals after discharge from the hospital. Long-term patients undergo FOB with BAL and TBB every 3 to 6 months.

Results

Indications

Tables 3 and 4 list the indications for HLT and lung transplantation (LT), respectively. Most HLTs were performed for pulmonary vascular disease, either PPH (9 patients) or secondary to a congenital heart defect (ES) (8 patients). Three HLTs were performed for obstructive lung disease (alpha-1 antitrypsin deficiency [A1ATD]). One patient each had HLT for cystic fibrosis (age 5), lymphocytic interstitial pneumonitis (LIP) (age 6), and obliterative bronchiolitis (OB) from a viral infection (age 3). This child had been ventilator dependent since birth because of infant respiratory distress syndrome and bronchopulmonary dysplasia, when he developed superimposed OB.

Among patients undergoing LT, nine had obstructive airways disease (7 A1ATD, 2 COPD). Three had PPH, one in association with Histiocytosis X. Three had idiopathic pulmonary fibrosis, and one each had lymphangioleiomyomatosis, OB after previous HLT, ES from a ventricular septal defect, cystic fibrosis, and LIP. There have been two retransplants; one, a SLT in a 10-year-old girl 2 years status post HLT who developed OB, and the other in a 17-year-old girl 1 month after unsuccessful SLT for LIP. The original allografted lung demonstrated refractory rejection as well as OB.

TABLE 3. *Indications for Heart–Lung Transplant*

Underlying Disease	No. of Transplants
Primary pulmonary hypertension	9
Eisenmenger's syndrome	8
Emphysema due to alpha-1 antitrypsin deficiency	3
Cystic fibrosis	1
Lymphocytic interstitial pneumonitis	1
Bronchopulmonary dysplasia with obliterative bronchiolitis	1
Total	23

TABLE 4. *Indications for Lung Transplant*

Disease	No. of Patients	Transplant Procedure
Alpha-1 antitrypsin deficiency	6	SLT
	1	DLT
	1	BSLT
Primary pulmonary hypertension	3	SLT
VSD, pulmonary hypertension	1	VSD closure, SLT
Emphysema	1	SLT
Lymphangioleiomyomatosis	1	SLT
Lymphocytic intersitital pneumonitis	1	SLT
Idiopathic pulmonary fibrosis	3	SLT
Obliterative bronchiolitis	1	SLT
Refractory rejection	1	SLT
Cystic fibrosis	1	BSLT
Total	21	

SLT, single lung transplant; DLT, double lung transplant; BSLT, bilateral single lung transplant; VSD, ventricular septal defect.

Waiting Times

Time on the waiting list was compared between patients undergoing HLT and those undergoing SLT as well as all lung-only transplants. As shown in Figure 4, the waiting time for SLT was 150 ± 42 days, compared with 384 ± 88 days for HLT ($p < 0.02$). Waiting time for all lung-only transplants was 166 ± 39 days ($p < 0.03$, compared with HLT).

Operative Procedures

Table 5 lists the operative procedures that have been performed in the patients in our series. There have been 23 HLTs, and in three instances, the recipient's heart has been transplanted into another individual (the so-called "dominoe" living donor procedure, as reported by Baumgartner et al.[9]) Seventeen patients have received 18 SLTs. Three patients have undergone bilateral lung replacement, one with an *en bloc* double-lung, and two with bilateral single-lung transplants.

Operative Survival

There has been one death within 30 days of transplant among HLT patients (4%). This death was due to uncontrollable hemorrhage in a 45-year-old man with a patent ductus arteriosus. All other HLT patients have been long-term survivors. Among LT patients, there have been four deaths within 30 days of transplant (19%). One death was due to cerebral hypoxemia from an intraoperative cardiac arrest. Another was due to poor pulmonary preservation (the first LT patient in our series). One patient had a massive pulmonary embolus to the transplant lung on postoperative day 4 and subsequently died. The final death was in the patient with ES from a ventricular septal defect (VSD). He had unsuspected right ventricular outflow tract

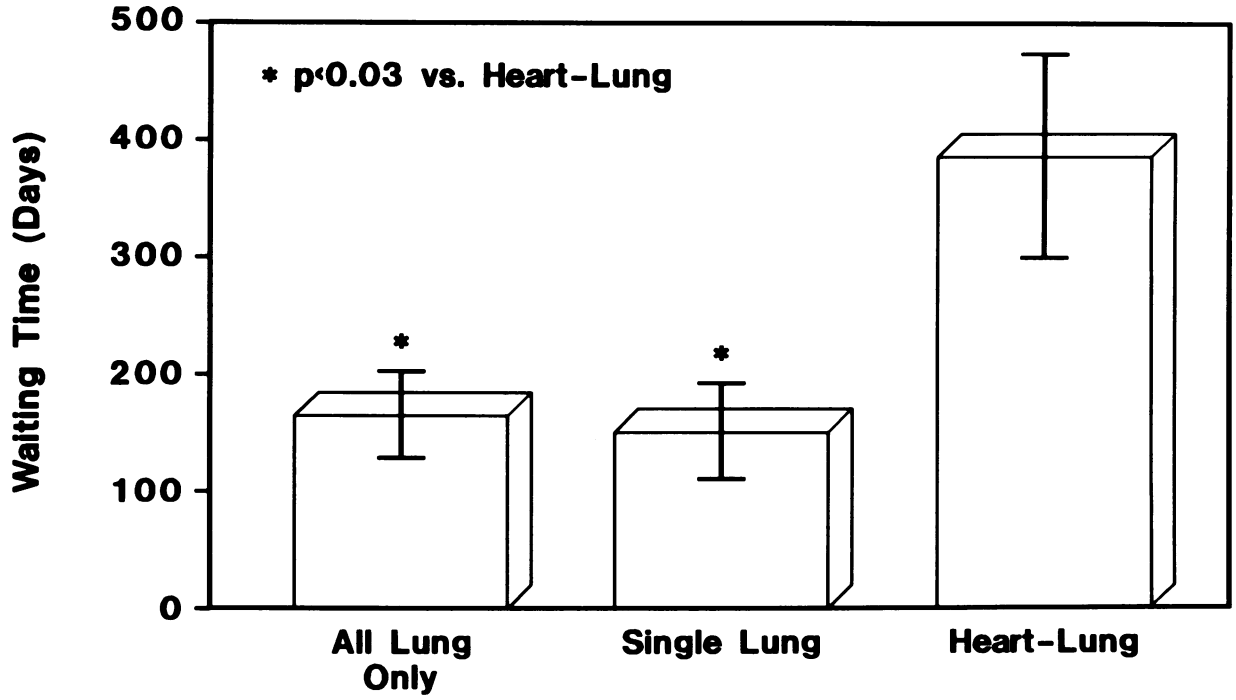

FIG. 4. Comparison of waiting times (mean ± SE) for all lung-only, single lung, and heart-lung transplant recipients.

obstruction, which was unmasked by SLT and closure of his VSD. He died because of low cardiac output from this right-sided obstructive lesion.

Pediatric Lung and Heart-Lung Transplantation

Six children have undergone a total of eight HLT and SLT procedures. These children ranged in age from 3 years to 17 years (mean, 7.3 years). Table 6 lists the diagnosis, patient age, and procedure. All procedures were performed on cardiopulmonary bypass. There has been one death. This occurred in a 10 year-old who had HLT for PPH at age 8. She developed OB and subsequently underwent SLT. She sustained an intraoperative cardiac arrest before the institution of cardiopulmonary bypass and died 5 days postoperatively of cerebral hypoxia. The other five patients are alive at 4 to 22 months after transplant. One child, a 4 year-old SLT for PPH, is awaiting retransplant for OB. Another, a 5 year-old HLT for lymphocytic interstitial pneumonitis, developed a lymphoproliferative disorder in the allograft lung. This has responded to gamma-globulin and alpha-interferon therapy. In addition, this child has evidence of recurrence of his original disease in his transplanted lungs. There has been one successful retransplant in a 17-year-old SLT recipient who developed refractory rejection and OB in her first allograft at 1 month after her first transplant. Three of the six patients are well, active, and not requiring supplemental oxygen.

TABLE 5. *Operative Procedures*

Procedure	No.
Heart-lung trasnplant—three dominoe procedures	23
Single lung transplant—one retransplant at 1 mo	18
Double lung transplant	1
Bilateral single lung transplant	2
Total	44

TABLE 6. *Pediatric Lung, Heart-Lung Transplant*

Diagnosis	Age (yr)	Procedure	Status
PPH	8	HLT*	OB at 18 mo, retransplant at 2 yr
PPH	4	SLT†	OB at 3 mo
Cystic fibrosis	5	HLT	A&W
LIP	5	HLT	Lymphoma at 3 mo, recurrent LIP at 1 yr
LIP	17	SLT	Refractory rejection, retransplant at 1 mo
OB	3	HLT	A&W, stenosis at tracheal anastomosis
OB (patient 1 above)	10	SLT	Died perioperatively
Allograft rejection (patient 5 above)	17	SLT, repeat	A&W 15 mo after second transplant

PPH, primary pulmonary hypertension; HLT, heart-lung transplant; OB, obliterative bronchiolitis; SLT, single lung transplant; A&W, alive and well; LIP, lymphocytic interstitial pneumonitis.

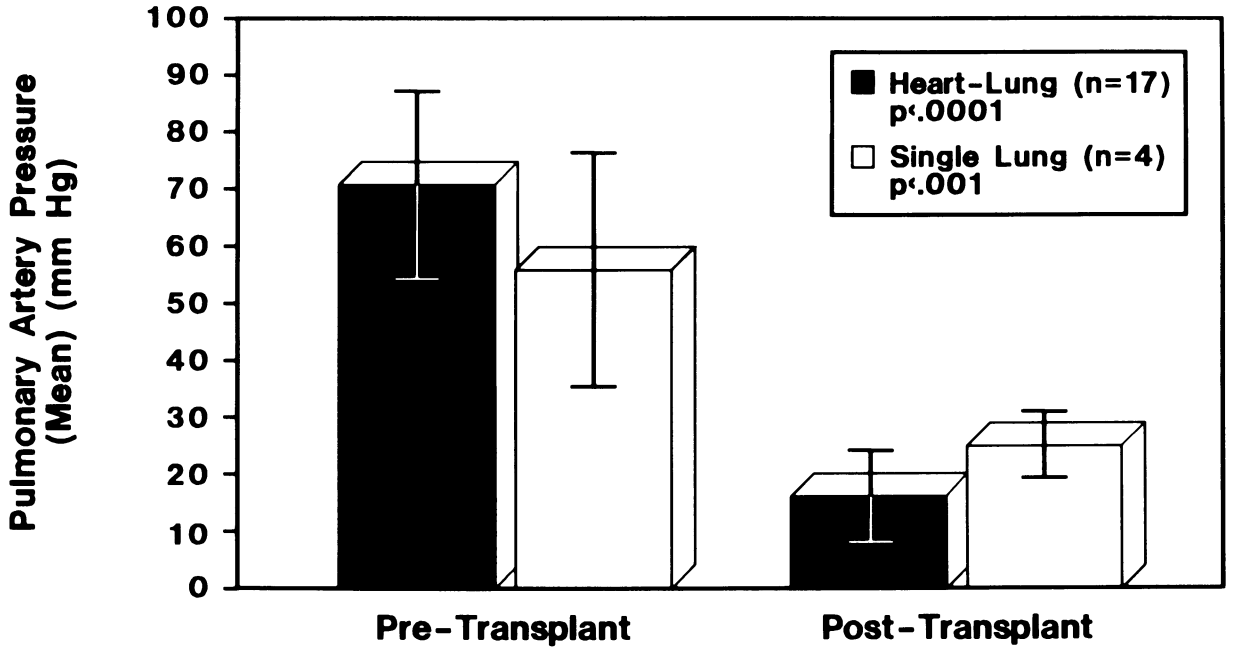

FIG. 5. Pulmonary artery pressures before and after heart–lung or single lung transplant for primary or secondary pulmonary hypertension.

Pulmonary Artery Pressures

There have been 17 HLTs and 4 SLTs performed for pulmonary hypertension, either primary (PPH) or secondary (ES). Figure 5 depicts the relative efficacy of these two procedures in lowering the mean pulmonary artery pressure (mPAP) after surgery. In the HLT patients, preoperative mPAP was 70 ± 17 mm Hg, and postoperative mPAP was 18 ± 9 mm Hg ($p < 0.0001$). In SLT recipients, preoperative mPAP was 57 ± 21 mm Hg and came down to 25 ± 5 mm Hg postoperatively ($p < 0.001$). Thus both procedures are capable of effecting a highly significant

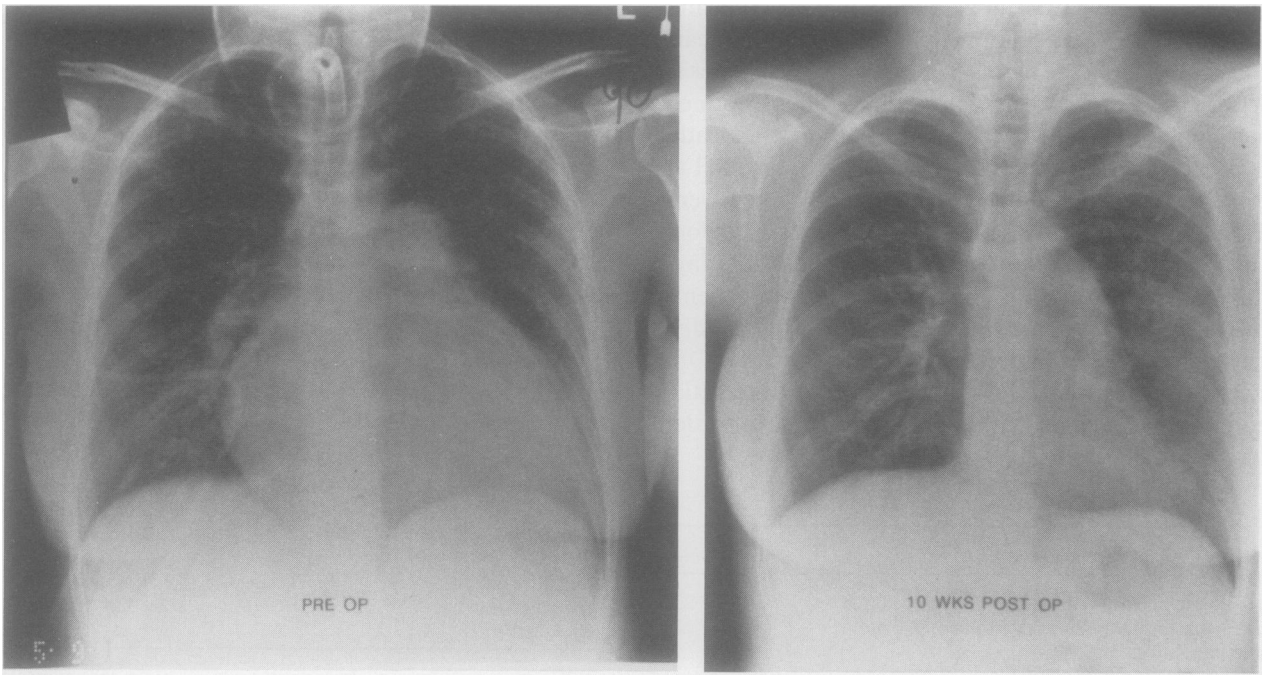

FIG. 6. Chest x-rays of a 27-year-old woman who received a right single lung transplant for primary pulmonary hypertension. Left, preoperative; right, 10 weeks postoperative.

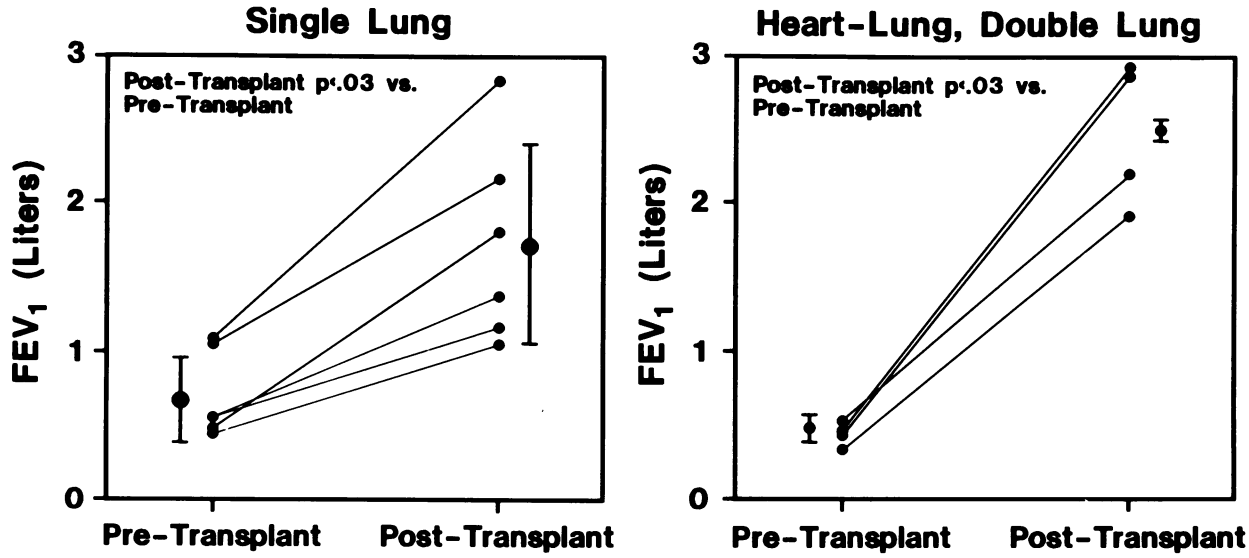

FIG. 7. Preoperative and postoperative FEV_1 in patients receiving (left) single lung and (right) heart–lung transplants for obstructive airway disease.

decrease in mPAP in patients with severe degrees of pulmonary hypertension. One instructive case is illustrated in Figure 6. This 27-year-old woman had pulmonary hypertension due to histiocytosis X. She had severe right ventricular failure and required tracheostomy for respiratory support before her transplant. She was awaiting a HLT; however it was decided to perform a SLT because of the greater likelihood of finding a donor. Single-lung transplantation was performed on cardiopulmonary bypass and she had an excellent result. Figure 6 compares her preoperative chest radiograph with one taken 10 weeks postoperatively. The heart size has returned to normal, the tracheostomy tube has been removed, and the allografted right lung appears normal radiographically.

Pulmonary Function

Three HLT and nine LT recipients (7 SLT, 1 double, 1 bilateral SLT) have undergone transplantation for obstructive airways disease (OAD). One SLT recipient died early after transplant of a pulmonary embolus. All remaining patients are long-term survivors. Examining this group in its entirety, these procedures are efficacious in improving pulmonary function as measured by forced expiratory volume in 1 second (FEV_1). Mean preoperative FEV_1 was 0.60 ± 0.25 L and improved to 2.03 ± 0.70 L after transplant ($p < 0.0001$). Figure 7 demonstrates the comparative benefit of HLT and SLT in effecting a satisfactory improvement in pulmonary function in patients with OAD. Single-lung transplant patients had a mean pretransplant FEV_1 of 0.69 ± 0.29 L. This improved to a mean of 1.73 ± 0.67 L post-transplant ($p < 0.03$), an improvement of 150%. Patients undergoing bilateral lung replacement (HLT, double, or bilateral single) had a mean pretransplant FEV_1 of 0.46 ± 0.08 L, improving to a mean of 2.49 ± 0.51 L post-transplant, an increase of over 400%.

Although patients receiving bilateral lung replacement enjoyed a significantly greater incremental increase in FEV_1 than patients receiving unilateral lung replacement (2.03 ± 0.48 L for bilateral *vs.* 1.04 ± 0.46 L for unilateral, $p < 0.03$), SLT recipients have experienced very satisfactory rehabilitation after transplantation. Figure 8 demonstrates the results of exercise testing performed in a group of five SLT and six HLT recipients. Comparing oxygen comsumption ($\dot{V}O_2$, ml/min) before and after exercise, recipients of one lung and recipients of two lungs demonstrate virtually equivalent increases in cardiovascular function.

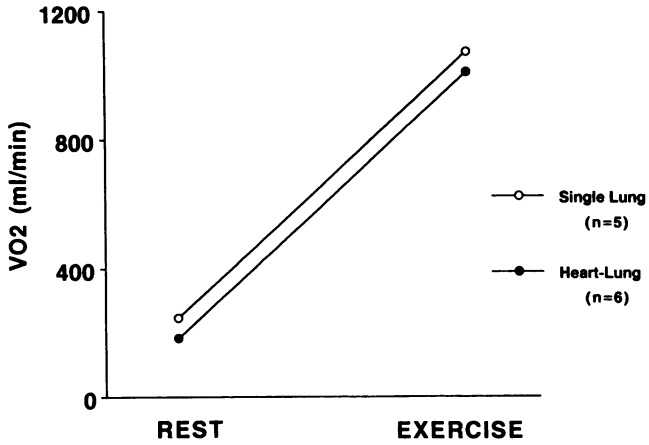

FIG. 8. Comparison of exercise testing results after single lung or heart–lung transplant (oxygen consumption, VO_2, ml/min).

Survival

Figure 9 depicts Kaplan-Meier survival of all HLT and LT patients. Survival is 82% and 73% at 1 and 2 years, respectively. Figure 10 compares survival of HLT patients with that of LT patients. Heart–lung transplant recipients experienced survival of 85% and 74% at 1 and 2 years, respectively. Recipients of LT have enjoyed survival of 80% at 1 and 2 years (p = NS relative to HLT).

Management of the Airway Anastomosis (es)

Heart–Lung Transplants. The tracheal anastomoses in the HLT recipients was not reinforced in 17 of the 23 patients. In the remaining six patients, the anastomosis was wrapped; with omentum in one and with donor pericardium in the remainder. There has been only one airway problem, an incidence of 4%. This was a contained dehiscence 4 to 5 weeks post-transplant in a 3-year-old patient. This child had been ventilator dependent for his entire life as a consequence of bronchopulmonary dysplasia. He had been receiving steroid therapy for reactive airways disease until approximately 4 weeks before his transplant. In addition he had severe tracheobronchial malacia involving the distal trachea and mainstem bronchi. The anastomosis was performed with interrupted absorbable suture material, and was wrapped with donor pericardium. He has required multiple bronchoscopies with balloon dilatation and laser therapy, and is awaiting implantation of a Silastic Y stent. Nonetheless, he is off the ventilator and walking, both for the first time in his life. His allografted organs are functioning normally.

Lung Transplants. Of 22 anastomoses in 20 LT recipients (two patients had bilateral SLT), 17 were reinforced with an omental pedicle graft traversing the diaphragm. One patient with previous abdominal surgery had the anastomosis wrapped with an internal mammary artery pedicle graft. Four anastomoses were unprotected. Anastomoses were performed in interrupted fashion with either absorbable or nonabsorbable suture material. In recent

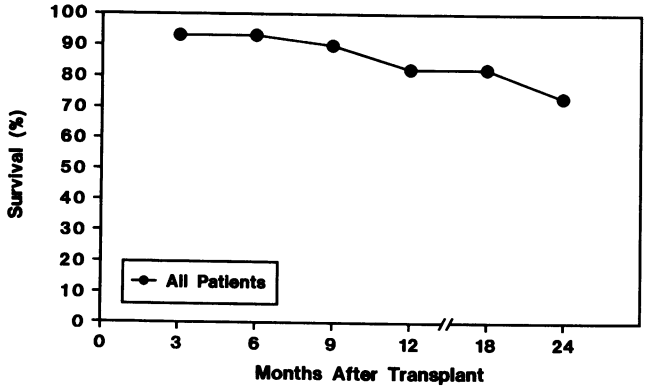

FIG. 9. Kaplan–Meier survival of all patients undergoing lung or heart–lung transplant.

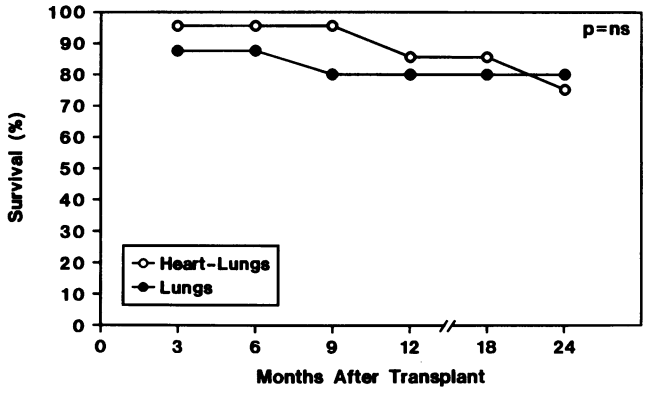

FIG. 10. Comparison of Kaplan–Meier survival of patients after lung-only and heart–lung transplant.

patients, an attempt has been made to telescope the donor bronchus into the recipient bronchus for the space of at least one cartilaginous ring. Of 17 anastomoses in 16 patients who have survived surgery and are at least 3 months post-transplant, there have been two that have demonstrated cicatricial narrowing. This represents an incidence of 11.7%. One was a patient, the first successful SLT in our series, who had a right SLT with bronchial omentopexy for lymphangioleiomyomatosis. She developed anastomotic narrowing at approximately 3 months after her transplant. She has had improvement and stabilization of her airway after aggressive rigid and fiberoptic bronchoscopy with dilatation and laser therapy. Somewhat disappointing has been the fact that her pulmonary function has not improved as much as expected given the restored patency of her airway. The other airway problem is in a 36-year-old man who underwent bilateral SLT for cystic fibrosis. At approximately 3 months after surgery, he developed stenosis at the site of his left bronchial anastomosis. Of interest is the fact that this very thin individual had insufficient omentum to reach both bronchial anastomoses. Therefore only the right bronchial anastomosis was wrapped with omentum, and this anastomosis is widely patent, whereas the contralateral, unprotected anastomosis has strictured. This patient has responded favorably to repeated balloon dilatation.

Other Complications

Return to the operating room for hemorrhage was required in 4 of 44 procedures (9%). One patient developed mediastinitis with a mycoplasma organism after HLT. This individual required multiple procedures for drainage of his mediastinum and pleura, but survived after a prolonged course. Another patient developed empyema after HLT. This responded to tube thoracostomy followed by rib resection with complete resolution. Two patients had herniation of abdominal viscera into the chest through the opening created for passage of the omental pedicle

graft. Both patients required emergency surgery, and in one, a colostomy was necessary to decompress a massively dilated colon. Two patients sustained phrenic nerve injuries. One appeared early and plication was necessary to allow separation from the ventilator. The other case appeared several weeks after transplant. Plication was performed and resulted in an improvement in function in the allografted lung.

One patient, an HLT recipient, developed severe pulmonary edema with reperfusion of her graft, and required extracorporeal membrane oxygenator (ECMO) support for 48 hours. She was successfully weaned from ECMO, and is a long-term survivor.

Perioperative Pulmonary Dysfunction

In an attempt to improve the diagnostic accuracy of perioperative pulmonary dysfunction in patients after lung and heart–lung transplantation, a program of frequent FOB with BAL and TBB was instituted. Sixteen transplants in 15 patients were studied during a total of 28 episodes of perioperative pulmonary dysfunction. Lung allograft preservation injury occurred in five instances. There were 14 episodes of clinical lung rejection. This was confirmed by TBB histology in nine of the cases. Infectious causes were elicited in 12 instances. Of note is the fact that bronchoscopy yielded information not expected from the initial evaluation in 10 instances (39% of the episodes). Employing the above studies for indications including new onset of pulmonary symptoms, increase in the alveolar-to-arterial oxygen gradient, or any change in the chest radiograph, this approach yielded a sensitivity of 79% and a specificity of 100% in the diagnosis of perioperative pulmonary dysfunction.[10]

Obliterative Bronchiolitis

Five patients have developed obliterative bronchiolitis (OB) after HLT (23% of survivors), and all have died at intervals of 1 to 2 years post-transplant. Three patients after SLT (19% of survivors) have evidence of OB within 3 to 10 months of transplant, and one patient has died. Of particular interest is the fact that all but one of these eight patients had pulmonary hypertension as the underlying diagnosis necessitating their transplant. Four of the five HLT and all three SLT recipients had primary or secondary pulmonary hypertension before transplantation. The single exception occurred in a 53-year-old lady with emphysema due to A1ATD. This lady underwent HLT and expired from OB at 1 year post-transplant.

Discussion

The concept of transplantation of pulmonary tissue as a therapeutic modality in the treatment of end-stage lung disorders was introduced by the successful engraftment of combined heart–lung blocks, first reported by Reitz et al.[1] As catalogued so well by Cooper et al.,[2] previous attempts at transplanting the lung had resulted in a litany of failures, due almost exclusively to inadequate healing of the airway anastomosis.[11] The cases reported by Reitz et al. represent a landmark in the annals of thoracic transplantation. Airway healing was uniform, and long-term survival with allografted lungs was shown to be feasible. Although plagued with problems of insufficient donors and the development of recurrent respiratory insufficiency due to bronchiolitis obliterans, heart–lung transplantation indisputably provided the latticework on which all subsequent developments in pulmonary transplantation have become interwoven.

The indications for lung and heart–lung transplantation continue to evolve. Certain trends, however, are beginning to emerge. The data in the current series regarding waiting times before transplant indicate a strong advantage in favor of single-lung *versus* heart–lung transplantation. Patients awaiting SLT waited 150 days, compared with 384 days for those awaiting HLT. This clear trend will have increasing ramifications for patient selection in the future. Individuals awaiting bilateral lung replacement can expect a longer wait before undergoing transplantation; however the wait still should be substantially shorter than that accompanying HLT. The explosion in the number of hospitals performing heart transplantation has virtually precluded the possibility of obtaining heart–lung blocs for transplantation, because the demand for suitable donor hearts has increased so dramatically that most donor hearts are implanted in waiting heart recipients. Lung transplantation, either single or bilateral, has demonstrated its ability to benefit patients with an increasingly wide range of pulmonary disorders. Originally introduced to treat patients with primarily restrictive pulmonary diseases,[2,11,12] lung transplantation has now been applied successfully to patients with obstructive diseases,[13,14] pulmonary sepsis,[7,15] and pulmonary vascular disease,[16,17] to name a few. These latter pathologies formerly were thought to require combined heart and lung replacement instead of lung-only replacement.

The Operations

The program at the University of Minnesota has had experience with 23 heart–lung and 21 lung transplant procedures. Certain technical features have become apparent that improve the safety of these operations. In the HLT procedure, we have found it expeditious to employ the TA-90 stapler to divide the pulmonary hila. This not only facilitates recipient pneumonectomy, but improves hemostasis as well. There has been only one death within 30 days in our 23 heart–lung recipients, an operative mortality rate of 4%. All other patients have been long-term survivors.

In the lung transplant recipient, it is important to have an intimate familiarity with the various methods of instituting cardiopulmonary bypass. Although many procedures can be performed without the need of extracorporeal support of the heart and lungs, in those cases where this support is necessary, the surgeon must be able to expeditiously institute cardiopulmonary bypass in a safe and effective manner. Situations that mandate bypass include hypercarbia with acidosis that cannot be controlled with buffers, hypoxia below 50 mm Hg, and any sign of circulatory instability. One maneuver that we have found helpful is to encircle the ipsilateral pulmonary artery as soon as possible after the lung is deflated after clamping of the endotracheal tube to that lung. This prevents shunting of a large amount of desaturated blood to an unventilated lung, and the attendant hypoxemia. In the child or the small adult, cardiopulmonary bypass requires cannulation of structures in the chest, and planning of the operation must take this into consideration. The choice of incision for lung transplantation is decided based on several factors. Single-lung transplantation in the adult is best performed through an anterolateral thoracotomy, with the ipsilateral femoral vessels available, should bypass be necessary, as described by Cooper et al.[2] In the child, the best approach is determined by body size, the likelihood of needing extracorporeal circulation, previous surgery, and the presence or absence of a tracheostomy. It behooves the transplant surgeon to be comfortable with a variety of approaches, because some ingenuity is required to choose the best approach for a given situation. The bilateral transverse thoracotomy described by Pasque et al.[7] is of great utility in a variety of circumstances. This incision provides excellent exposure to the structures of the mediastinum, as well as to the lungs, pleural spaces, and pulmonary hila. This approach has been employed in our series for bilateral SLT, as well as for right and left SLT. In those instances in which bilateral transverse thoracotomy has been used for SLTs, there has been the need for concomitant cardiopulmonary bypass, in one case for pulmonary hypertension and in another for associated repair of an intracardiac defect associated with pulmonary hypertension. The other option that should not be overlooked for SLT is that of midline sternotomy. This incision provides good exposure to the right pulmonary hilum for right SLT, and institution of cardiopulmonary bypass (CPB) is straightforward, should it be needed. Using the operative techniques described, we have had four perioperative deaths in the first 21 lung transplant procedures.

Pediatric Lung and Heart–Lung Transplantation

The pediatric lung and heart–lung transplant series reported herein represents the largest experience reported to date. Several lessons have already been learned in this group of patients. Most importantly, both lung and heart–lung transplantation are technically feasible in children at least as young as 3 years (HLT) and 4 years (SLT), respectively. Cardiopulmonary bypass appears to be more uniformly required to achieve safe transplantation in the pediatric age group. Furthermore CPB can less reliably be effectively instituted through the femoral route in children. Therefore the planning of the operative approach must allow for the possibility of CPB through the chest. Retransplantation, either early or late after the initial procedure, has proven technically feasible, if somewhat difficult. Five of our 7 patients are alive 4 to 22 months after transplant. One is still receiving treatment for cicatricial narrowing at the tracheal anastomosis (HLT), but is doing very well overall with excellent graft function. This patient had been ventilator dependent and on steroid therapy for the entire 3 years of his life before transplant, and is currently off the ventilator and walking, both for the first time in his life. Another, a 4 year-old SLT for PPH, has developed OB, and is awaiting retransplant. Another child, an HLT at age 5 for lymphocytic interstitial pneumonitis, has had a lymphoproliferative process in one of his allografted lungs that has responded well to alpha-interferon and gamma-globulin. He has a recurrent infiltrative process in his lungs, which on biopsy appears very similar to his presenting pathologic process. The remaining two patients are well, without evidence of OB or recurrent disease.

Pulmonary Artery Pressures

The data presented herein indicate that lung and heart–lung transplantation are equally effective in the treatment of elevated pulmonary artery pressures due to primary pulmonary hypertension. Limited experience also suggests that the two procedures are efficacious in reversing elevated pulmonary artery pressures occurring secondary to a congenital heart defect with increased pulmonary blood flow (Eisenmenger's syndrome). The experience gained in this group of patients has provided critical information regarding the ability of SLT to replace HLT in the treatment of individuals with pulmonary hypertension from a variety of causes. The knowledge that SLT and HLT are equally effective in reversing elevated pulmonary artery pressures provides a major incentive to apply SLT in these cases, because many more patients can potentially benefit from SLT, for any given number of donors. An area of great interest remains the application of repair of congenital heart defects in conjunction with SLT. This operation has been successfully accomplished for simple defects (patent ductus arteriosus).[17] For more complex defects, however, the utility of this approach remains speculative. The case we report of a VSD repair and concomitant SLT proved quite feasible technically, and was accomplished with a very acceptable period of allograft ischemia. Nonetheless this individual succumbed to a combination of low cardiac output and a poorly functioning donor lung. Clearly the right ventricular pathology

proved more complex than we had appreciated, and the postoperative course was greatly complicated by the development of right-ventricular outflow tract obstruction and low forward cardiac output. No doubt this group of patients can benefit from SLT; however selection must be carefully performed, and cardiac evaluation must be scrupulously thorough, so that all cardiac defects may be corrected at the time of transplant.

Pulmonary Function

In patients afflicted with pulmonary parenchymal diseases, the goal of lung replacement is to increase pulmonary function and to improve exercise capacity. Cooper, Patterson, and others have reported the dramatic reversal in lung dysfunction that can accompany successful lung transplantation, initially in patients with pulmonary fibrosis.[2,11,12] Until recently there was concern that OAD would require bilateral lung replacement. This concern related to fears of overinflation of the remaining native lung with compression of the transplanted lung, if single-lung replacement were performed. Several authors have now reported successful SLT for OAD, and the worries regarding problems with the native lung have proven largely unfounded.[14,18] In the current series, there are 12 patients who received transplants for OAD. Three patients received HLT and nine, LT, either single or bilateral. Both LT and HLT proved efficacious in providing increased lung function after transplantation. As expected, patients receiving two lungs experienced greater improvement in lung function than those receiving one lung (400% *vs.* 150% increase in FEV_1). Nonetheless SLT recipients have enjoyed cardiovascular rehabilitation after transplantation that is virtually indistinguishable from that experienced by recipients of bilateral lung replacement.

Survival

A critical factor in any comparison of procedures is that of survival. Clearly if one procedure proves vastly superior in this vital outcome area, this single fact would outweigh many lesser advantages of any procedure with which it is being compared. Survival after any lung transplant procedure in the current series is 82% and 73% at 1 and 2 years, respectively. Patients undergoing HLT have Kaplan-Meier survival of 85% and 74% at 1 and 2 years, respectively, compared with 80% at 1 and 2 years for recipients of LT (p = NS). Data in both groups are intermediate, at best, because the majority of procedures have been performed in the past 2 years. Nonetheless lung and heart–lung transplantation appear to be very similar relative to patient survival in the short-to-intermediate term after transplantation.

Airway Anastomosis

The airway anastomosis was, for many years, the primary obstacle to successful engraftment of transplanted lungs. Work by the Toronto group resulted in the use of the omental pedicle graft to reinforce the bronchial anastomosis, and to allow ingrowth of new blood vessels to this poorly vascularized structure.[19,20] This work, coupled with the demonstration by Reitz et al. that long-term survival with allografted lungs was feasible,[1] brought closer the day of successful single lung transplantation. The availability of improved immunosuppression in the form of cyclosporine was also highly instrumental in allowing successful engraftment of both lung and heart–lung grafts. Thus a combination of factors converged to eventuate in the realization of the elusive dream of transplanting the human lung. It remains our preference to employ the omentum whenever it is available for wrapping the airway anastomosis in lung or bilateral lung transplants. In heart–lung transplant procedures, the anastomosis is wrapped with donor pericardium when it is available. Most HLT anastomoses have not been reinforced. Attempts also are made to telescope the donor bronchus into the recipient bronchus for the distance of one cartilaginous ring, after the method described by Veith et al.[21] and popularized by Trinkle.[16] This is particularly important when the omentum is not available.

Other Complications

As expected, surgery of the magnitude of lung or heart–lung transplantation is attended by complications. Nine per cent of patients required return to the operating room for hemorrhage. All these patients had required cardiopulmonary bypass for the performance of their transplant (2 SLT, 1 HLT, 1 bilateral SLT). Two patients have developed intrathoracic infections, one early and one late, both after HLT. Both cases responded to aggressive drainage and antibiotic therapy. Gratifyingly there have been no infectious deaths in the entire series. The omental pedicle graft has proven to be a mixed blessing in our hands. Two patients have had herniation of transverse colon into the left chest through the opening made to pass the omentum. Both have required reoperation to repair the diaphragmatic defect, and one required colostomy to decompress a massively dilated transverse colon and cecum. Phrenic nerve injury also has occurred and has been associated with significant morbidity and prolongation of the hospital course.

Perioperative pulmonary dysfunction can present either early or late after transplant. Two HLT recipients have required ECMO in the early postoperative period for pulmonary dysfunction. One was successfully weaned from ECMO support at 48 hours, and is a long-term survivor. The other individual had massive, uncontrollable hemorrhage necessitating large-volume transfusion of blood products. This resulted in pulmonary edema, and ECMO had to be employed. This patient died at day 4 of ongoing, uncontrolled hemorrhage, despite multiple reoperations, arteriography, and attempted embolization of posterior

mediastinal bleeding points. Pulmonary dysfunction occurring later has responded to an aggressive diagnostic and therapeutic protocol based on frequent FOB, combined with TBB and BAL. Liberal use of these modalities has yielded a sensitivity of 79% and a specificity of 100% in the diagnosis of perioperative pulmonary dysfunction.[10]

Obliterative Bronchiolitis

Obliterative bronchiolitis (OB) has long been recognized as the main impediment to long-term survival after heart–lung transplantation. Despite premature claims to the contrary, however, it is now clear that recipients of lung grafts can expect to experience an approximately equal incidence of this devastating disorder. LoCicero et al.[22] describe an unequivocal case of OB occurring 9 months after SLT in a patient who eventually died of this disorder.[22] McGregor et al.[23] also have reported the occurrence of OB after isolated SLT. In the current series of patients, OB has occurred in five patients after HLT (23%), and in three long-term survivors of LT (19%). All patients developing OB after HLT have died as a result of this process. One of the three LT patients with OB has died, and the remaining two are awaiting retransplant. Of particular interest is the fact that 7 of the 8 patients who have developed OB have had pulmonary hypertension as the diagnosis necessitating transplantation.

Summary and Conclusions

Lung and heart–lung transplantation are established therapeutic modalities for the treatment of end-stage pulmonary and cardiopulmonary disorders. The current experience at a single institution discloses certain information of importance to the field of thoracic transplantation. Lung transplantation, either single or bilateral single, can safely and effectively be applied to diseases formerly thought treatable only by heart and lung replacement. Most notable among these diseases are the obstructive airways diseases and diseases involving irreversible elevation of the pulmonary artery pressures. The operative safety of lung transplantation compares favorably with that of heart–lung transplantation. Furthermore the incidence of airway complications, although somewhat higher after LT, is not prohibitively so. Indeed, Levine, of Trinkle's group has reported successful SLT in a significant number of patients without the use of an omental pedicle graft with no airway complications.[16] A point that has emerged very clearly is the fact that patients awaiting lung transplants can expect a far shorter waiting time before transplant than those awaiting heart–lung transplants. Also because three individual recipients can potentially benefit from a single donor with donation of each of the two lungs as well as the heart, lung transplantation results in a better usage of scarce donor organs. For all these reasons, lung transplantation should be the procedure of choice whenever possible for individuals with end-stage lung disease. Heart–lung replacement still has a role in the treatment of patients with combined heart and lung disease in situations in which the heart is unable to be repaired.

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