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A Decade of Lung Transplantation

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Objective

The experience accrued at the University of Pittsburgh between March 1982 and December 1992 in the various forms of lung transplantation, including heart-lung, double lung, and single lung, is discussed.

Summary Background Data

Heart-lung (n = 97) was the most commonly performed operation followed by double lung (n = 80) and single lung (n = 68). Major indications included primary pulmonary hypertension (n = 76), obstructive lung disease (n = 57), Eisenmenger's syndrome (n = 42), cystic fibrosis (n = 32), and retransplantation (n = 13). Since May 1991, 115 procedures have been performed and heart-lung transplantation has decreased from 61% to 15% of the cases with a corresponding doubling in double lung from 24% to 43% and single lung from 15% to 42%.

Results

The 1-, 2-, and 5-year survival rates in all 232 recipients were 61%, 55%, and 44%, respectively. The actuarial survival rate was significantly better for those 107 recent recipients compared to the 125 early recipients (70% *vs.* 61%). Overall, the 63 single (70%) and 74 double (65%) lung procedures were more successful than heart-lung transplantation (53%). Recently, however, lung transplantation has been associated with an improvement in the survival rate from 48% to 72%. The survival rate has also improved from 53% to 77% for single lung transplant recipients. The causes of death in 106 recipients included infection (n = 40), early allograft dysfunction (n = 23), obliterative bronchiolitis (n = 13), and inoperative bleeding (n = 10). Poor outcomes also included technical problems (n = 6), lymphoma (n = 4), acute rejection (n = 3), diaphragmatic paralysis (n = 2), multisystem organ failure (n = 2), stroke (n = 2), liver failure (n = 1), and airway dehiscence (n = 1).

Conclusions

The long-term outlook for lung transplant recipients has improved. There appears to be significant conservation of organs with single lung and double lung transplantation, finding greater acceptance for diseases once exclusively treated by heart-lung transplantation alone. The improved long-term outlook will be dependent upon better treatment for chronic rejection of the airways that histologically is defined by obliterative bronchiolitis.

In the past decade, 245 lung transplants have been performed at the University of Pittsburgh. Our program began in 1982, shortly after the reported success of Reitz et al. with cardiopulmonary transplantation,[1] and has been favored by the broad-based institutional support of a multi-organ transplant effort.[2] Pulmonary transplantation in its various forms, including heart-lung,[3] single lung,[4] and double lung,[5] has become a reasonable thera-

peutic option for patients with end-stage pulmonary and cardiopulmonary diseases. Many changes have been implemented as experience and knowledge have grown. In this report, we emphasize our current thoughts and practices. For purposes of illustration, we compare early and recent experience arbitrarily, with "early" defined as the first 9 years (May 1982 to May 1991) and "recent" as the recent 19 months (June 1991 to December 1992). The groups are roughly comparable in size: early, 130 procedures; recent, 115 procedures. By June 1991, our program had evolved to regularly include double lung and single lung transplantation as options for most pulmonary and cardiopulmonary diseases and thus represents the most contemporary group from which to compare earlier experiences and to draw current standards.

PATIENT POPULATION AND PROCEDURE SELECTION

There were 232 patients who underwent 245 procedures between May 1982 and December 1992. Heart-lung transplantation (n = 97) was the most commonly performed operation followed by double lung (n = 80) and single lung (n = 68) replacement. Major indications in order of frequency included primary pulmonary hypertension (n = 76), obstructive lung disease (n = 57), Eisenmenger's syndrome (n = 42), cystic fibrosis (n = 32), retransplantation (n = 13), pulmonary fibrosis (n = 11), sarcoid (n = 6), lymphangiomyomatosis (n = 4), and miscellaneous (n = 4) (Table 1). There were 110 male and 135 female patients. The median age of the patients was 35.2 ± 12.4 years (standard deviation) (range, 1.3 to 66.4 years). Thirty-two of our recipients were younger than 18 years of age. The early experience included 130 procedures: 79 heart-lung (61%), 31 double lung (24%), and 20 single lung (15%). The recent group of 115 transplant procedures completed between June 1991 and December 1992 include a striking decrease in heart-lung (n = 18; 15%) and increases in both double lung (n = 49; 43%) and single lung (n = 48; 42%) transplants. Initially, primary pulmonary hypertension and Eisenmenger's syndrome were the most common indications for transplantation and were treated by heart-lung replacement (Table 1). Recently, treatment of obstructive disease by single lung transplantation has been the most common procedure, and attempts have been made to maximally utilize available organs for other indications previously treated by heart-lung transplantation. Accordingly, double and single lung procedures have increasingly been applied to primary vascular diseases and simple forms of Eisenmenger's syndrome (atrial septal defect [n = 4] and patent ductus arteriosus [n = 8]). The pulmonary insufficiency and sepsis of cystic fibrosis treated early by us in 1983 by heart-lung transplantation[6] has recently become a more common indication and is now treated solely by double lung replacement.

The major diseases treated in our pediatric group included cystic fibrosis (n = 9), primary pulmonary hypertension (n = 7), and Eisenmenger's syndrome (n = 7). Other conditions encountered were pulmonary arteriovenous malformation, desquamative interstitial pneumonitis (n = 2), graft *versus* host disease (n = 1), emphysema (n = 1), rheumatoid lung (n = 1), cardiomyopathy (n = 1), and Proteus syndrome (n = 1). Six (19%) of the children had previous sternotomy or major pulmonary resection by thoracotomy. There were 16 heart-lung, 14 double lung, and 2 single lung transplants performed in children.

SURGICAL PROCEDURES

Our current technique of heart-lung transplantation has evolved incrementally[3] and has benefitted from lessons learned from new approaches with double and single lung transplantation. Initially, exposure was by median sternotomy with anastomoses performed to the recipient's distal trachea, cuff of right atrium, and ascending aorta. Later the tracheal-to-supracarinal anastomosis was wrapped with a pedicle of omentum with the hope of reducing the rare but devastating complication of tracheal dehiscence or mycotic aneurysm of the juxtopositioned aortic suture line.[7] Exuberant use of ice slush and electrocautery in our early experience was reduced to lessen the risk of thermal injury to the phrenic nerves. We learned to avoid inadvertent proximal vagotomy, which earlier was common during dissection of the carina and posterior hilum, and recently the proximal left pulmonary artery was not removed because of the proximity of danger of injury to the recurrent laryngeal nerve. Because operative hemorrhage from the posterior recesses of the thorax and mediastinum became the most significant postoperative problem after heart-lung transplantation, we changed to a bilateral thoracotomy that had been introduced for double lung transplantation.[5] This incision through the anterolateral fourth intercostal space with transverse sternotomy provided considerably improved exposure to the chest and posterior hilar regions before and after cardiopulmonary bypass. Although a tracheal-to-supracarinal anastomosis

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Table 1. MAJOR INDICATIONS

	Early Group (5/82–5/91)			Recent Group (6/91–12/92)			
	H-L	DL	SL	H-L	DL	SL	Total (%)
PPH	47	7	2	7	5	8	76
Eisen	19	5	—	9	7	2	42
COPD	5	6	12	1	10	23	57
CF	1	10	—	—	21	—	32
IPF	2	1	3	—	2	3	11
ReTx	2	2	1	—	—	4	13
Sarcoid	1	—	1	—	4	4	6
LAM	—	—	1	—	—	3	4
Other	1*	—	—	2†	—	1‡	4
Total %	78 (0.1)	31 (0.24)	20 (0.15)	19 (0.16)	49 (0.41)	48 (0.42)	245 (1.0)

H-L: heart-lung; DL: double lung; SL; single lung; Eisen: Eisenmenger's syndrome; PPH: primary pulmonary hypertension; COPD: chronic obstructive pulmonary disease; CF: cystic fibrosis; IPF: idiopathic pulmonary fibrosis; LAM: lymphangiomyomatosis; ReTx: retransplant.

* Eosinophilic granuloma.

† Proteus syndrome (n = 1); cardiomyopathy (n = 1).

‡ Hard metal.

can be conveniently made through this approach, we now prefer to avoid mediastinal dissection altogether and perform the airway connections between the recipient's left and right main-stem bronchi as they emerge from the mediastinum. The donor's main bronchi are shortened to two cartilaginous rings above the upper lobe branches to reduce the risk of ischemic injury, which results from division of collaterals vessels. A telescoping, interrupted suture reported by Trinkle et al.[7] is now used, and the suture line is not wrapped by omentum or pericardial fat. Selective ventilation of the left and right lung through a double-lumen endotracheal tube permits a better view of the chest, hilum, and mediastinum for hemostasis.

Double lung transplantation was originally performed *en bloc* similar to heart-lung transplantation with cardiopulmonary bypass through a median sternotomy with a circumferential left atrial anastomosis, left atrium to donor atrial cuff performed intrapericardially, proximal recipient to distal donor main connections between main pulmonary arteries, and recipient trachea to the pericarinal airway of the donor.[9] Problems with ischemia of the bronchi and trachea around the carina led to the adoption of bilateral main-stem bronchial anastomoses. Exposure was improved by the anterior trans-sternal bilateral thoracotomy, and for diseases without associated pulmonary hypertension, cardiopulmonary bypass was avoided by sequencing bilateral single lung transplantation.[10] During replacement of the least perfused lung, the recipient can generally be sustained by ventilation of the contralateral lung, which in turn is removed when the first allograft is revascularized and ventilated.

Single lung transplantation is also generally performed without the use of cardiopulmonary bypass, unless the recipient suffers with a primary or secondary pulmonary hypertension. Ideally, the least perfused lung is transplanted. The allograft can be significantly oversized when the thorax is large due to obstructive lung disease. This is also done when the left lung is transplanted because the left diaphragm can be depressed into the abdomen without restriction from the liver. The airway anastomosis is performed as we have described.[7] Sutures are placed with care to insure widely patent nonrestrictive arterial and venous anastomoses, and donor and recipient arteries and veins are trimmed to avoid distortion of anastomoses.[11] As in double lung transplantation, a double lumen endotracheal tube permits contralateral ventilation during implantation and, as in heart-lung and double lung transplantation with cardiopulmonary bypass, is an aid in exposure for hemostasis.

IMMUNOSUPPRESSION

Immunosuppressive protocols have been based upon cyclosporine (blood level, 700 to 1000 ng/mL), azathioprine (1 to 2 mg/kg/d), and prednisone (0.2 mg/kg/d). Initially, rabbit antithymocyte globulin (RATG) prepared in our laboratory was given perioperatively to all recipients. Methylprednisolone (500 mg) is given just before revascularization of the allograft and 125 mg is delivered every 8 hours for three doses. Oral prednisone has been avoided for the first 14 to 21 days, except in those recipients who required supplements because of long-term preoperative steroid dependency. In the absence of

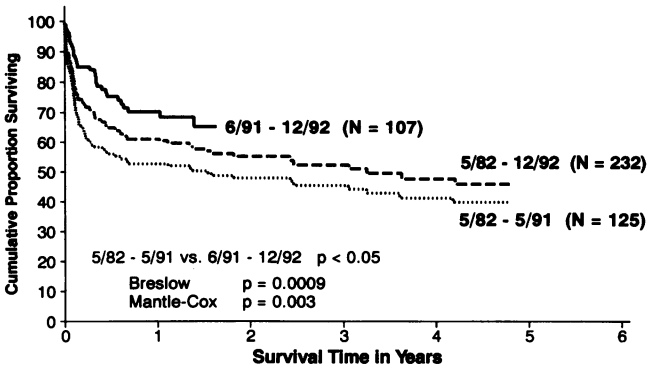


Figure 1. Pulmonary transplantation performed at the University of Pittsburgh. Survival by time interval.

repeated episodes of rejection, prednisone was weaned. Acute rejection was treated with three daily 1-g doses of methylprednisolone and, when rejection was recurrent, with RATG. Within the first 2 years of our program, we learned that rejection of the lung frequently occurred in the absence of cardiac rejection and that cardiac rejection virtually never occurred without histologic or radiographic changes in the lung.[12] This caused us to change our surveillance to include transbronchial biopsy and to delete endomyocardial biopsy for heart-lung recipients. When single lung and double lung transplantation were begun later, transbronchial biopsy was in place, and we had learned much about not only the histologic diagnosis of pulmonary rejection, but also its clinical and radiographic signs as well.

We recently studied the effects of the new immunosuppressant FK 506 on adult and pediatric patients. In the adults, a randomized comparison of, and in children a substitution for, cyclosporine is underway.

SURVIVAL

Overall and by Procedure

The 1-, 2-, and 5-year survival rates for all 232 recipients were 61%, 55%, and 44%, respectively (Fig. 1). The actuarial survival was significantly better for those 107 recent recipients compared to the 125 early ones (p = 0.0009, Breslow; p = 0.003, Mantel–Cox). The difference between the groups at 1 year was 70% *versus* 61% (Table 2). Overall, the 63 single lung (70%) and 74 double lung (65%) procedures were more successful than heart-lung transplantation (53%). In the recent group of 18 recipients, the survival rates for heart-lung transplantation have improved from 48% to 72% (Fig. 2, top left). Statistically significant increases in survival rates were also noted in single lung recipients (from 53% to 77%; p = 0.038, Breslow) (Fig. 2, top right). Similar improvement was not noted in the double lung recipients (66% *vs.* 63%) (Fig. 2, bottom).

By Disease

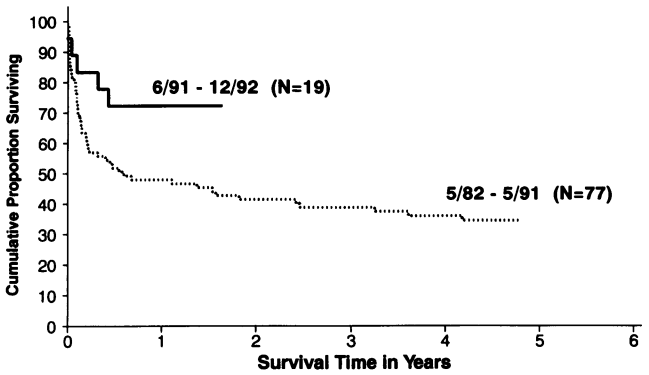
In the recent group, 1-year survival obtained in the major disease categories demonstrated an advantage for those 34 patients with obstructive lung disorders (79%) followed by 18 with primary pulmonary hypertension (76%), 21 with cystic fibrosis (62%), and 18 with Eisenmenger's syndrome (61%) (Fig. 3). The improved result in obstructive lung disease was significantly better than that obtained in the Eisenmenger group (p = 0.05, Breslow). The adverse impact of multiple resistant bacteria on the outcome of patients with cystic fibrosis was impressive. We detected an 84% survival rate in the antibiotic-sensitive recipients and only 40% in patients with resistant organisms. Of particular interest has been the rather uniform rate of survival in 36 patients with primary and secondary pulmonary hypertension who were treated by either heart-lung, double lung, or single lung transplantation (Table 3). In the hypertensive group, preoperative hemodynamics did not discriminate survivors from nonsurvivors of single, double, or heart-lung transplantation. The right ventricular ejection fraction rose in the survivors of single lung and double lung transplantation from below 29% to greater than 47%, and mean pulmonary artery pressure fell from 67 to 28 mmHg.

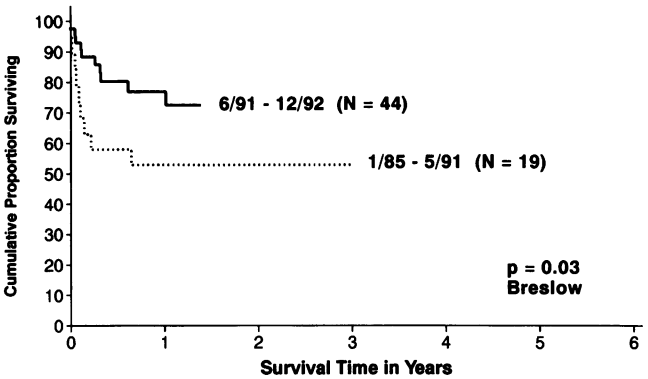
Pediatric

With a mean follow-up time of 1.8 years, the survival rate in the pediatric group was 78%. The 23 patients without cystic fibrosis fared much better than those 9 with the septic lung disease. Eighty-seven per cent of the former compared with 55% of the latter survived 1 year.

Table 2. ONE-YEAR SURVIVAL ACCORDING TO TYPE OF LUNG TRANSPLANT

	Heart-Lung	Single Lung	Double Lung	Total
Early (5/82–5/91)	48% (n = 77)	53% (n = 19)	66% (n = 29)	53% (n = 125)
Recent (6/91–12/92)	72% (n = 18)	77% (n = 44)	63% (n = 45)	70% (n = 107)
All (5/82–12/92)	53% (n = 95)	70% (n = 63)	65% (n = 74)	61% (n = 232)





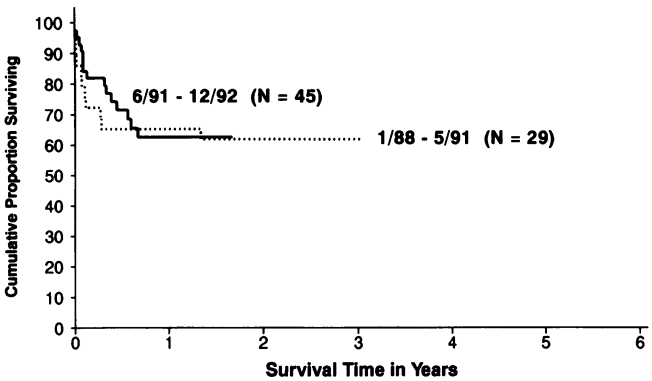


Figure 2. (Top left) Heart-lung transplantation performed at the University of Pittsburgh. Survival by time interval. (Top right) Single lung transplantation performed at the University of Pittsburgh. Survival by time interval. (Bottom) Double lung transplantation performed at the University of Pittsburgh. Survival by time interval.

CAUSES OF DEATH AND COMPLICATIONS

The causes of death in the 106 nonsurvivors indicate that infection (n = 40), early allograft dysfunction (n = 23), obliterative bronchiolitis (n = 13), and operative bleeding (n = 9) were the major problems. Poor outcomes also included technical problems (n = 6), lymphoma (n = 4), acute rejection (n = 3), diaphragmatic paralysis (n = 3), multi-system organ failure (n = 2), stroke (n = 2), liver failure (n = 1), and airway dehiscence (n = 1) (Table 4). In the early group, the highest percentage of deaths within the first 100 days after operation was due to early allograft dysfunction (37%) and infection (31%) (Fig. 4, top). In the recent group, allograft dysfunction was a less common cause (18%), but infection (35%) continued to be problematic. The main reasons for losses after 100 days included chronic rejection (46%) and infection (38%) in the early group and infections (64%) in the recent series (Fig. 4, bottom). The hazard rates (number of events per 1-month interval divided by the number of patients surviving at midpoint of that interval) for the major complications show that after the perioperative problems of bleeding and allograft dysfunction, infection and chronic rejection are continued risks (Fig. 5).

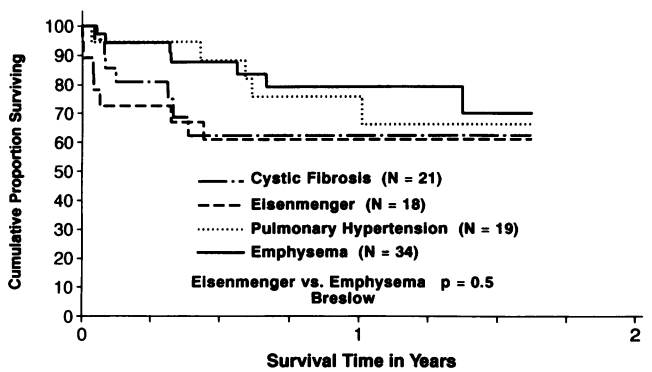


Figure 3. Pulmonary transplant survival by major disease.

Infection

Infections accounted for the majority of complications, and 80% arose within the allograft. Bacterial pneu-

Table 3. SURVIVAL ACCORDING TO PROCEDURE—PULMONARY HYPERTENSION

	Primary Pulmonary Hypertension	Eisenmenger's Syndrome	Total
Heart-lung	4 (alive)/6 (total)	6/9	10/15
Single lung	6/8	1/2	7/10
Double lung	4/5	4/7	8/12
Total	14/19	11/18	25/37

Table 4. 106 DEATHS AMONG 232 LUNG TRANSPLANTS (5/82–12/92)

Infection	40
Allograft dysfunction	23
Obliterative bronchiolitis	13
Bleeding	10
Technical	6
Lymphoma	4
Acute rejection	3
Diaphragm paralysis	2
Multisystem failure	2
Stroke	2
Liver failure	1
Airway dehiscence	1

monia was the most common infection (106 of 334 total infections; 32%) and was usually associated with gram-negative organisms (66 of 106 pneumonias). Cytomegaloviral (CMV) infection, which occurred in 48 of 118 patients (41%) at risk, was common and 27 of 48 of these

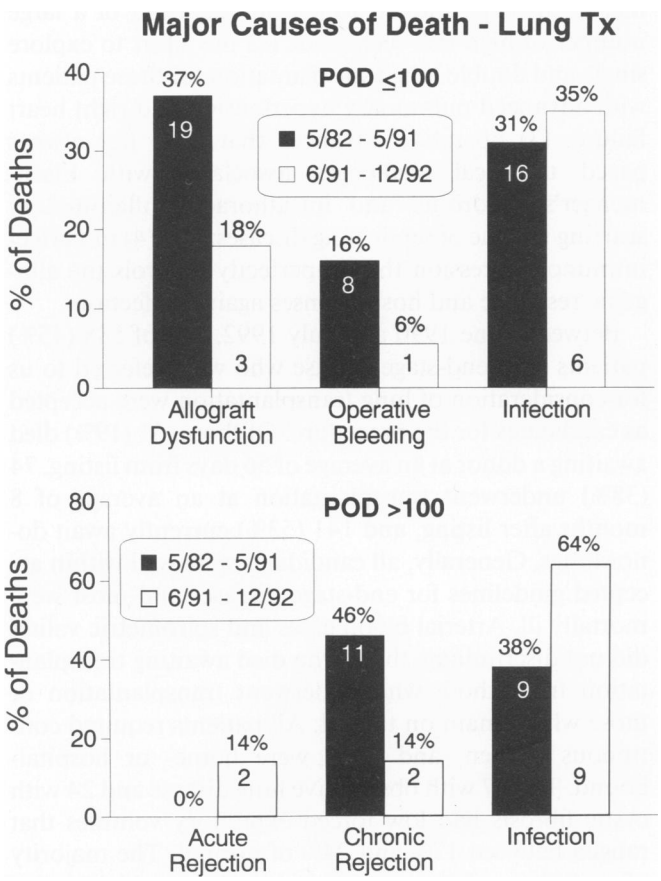


Figure 4. (Top) Pulmonary transplantation performed at the University of Pittsburgh. Major causes of death within first 100 days. (Bottom) Pulmonary transplantation performed at the University of Pittsburgh. Major causes of death after 100 days.

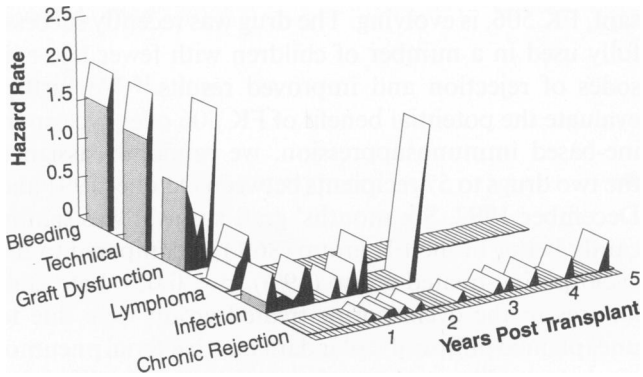


Figure 5. Causes of death—hazard rates.

cases (56%) were associated with pneumonia or disseminated infection. If the donor or recipient was sero-positive for CMV, the prevalence of infection was 87% and 71%, respectively. Infection in the sero-negative recipient was more likely to be symptomatic (95% *vs.* 45%) and fatal (45% *vs.* 10%). The other significant viral infection was Epstein-Barr virus, which resulted in post-transplant proliferative disease in 11 of 102 patients at risk. The infection resolved in all but three of these patients with reduced immunosuppression, but at the cost of later having obliterative bronchiolitis as a form of chronic rejection. Fungal infections also occurred (19 of 118; 14%) and were deadly (93% mortality rate). Thirteen of 19 fungal infections began in the allograft and were due to *Candida,*[11] Cryptococcus,[1] and *Aspergillus.*[7]

Acute Rejection

Sixty-nine patients who survived for a minimum of 5 days after single lung (n = 27), double lung (n = 32), or heart-lung (n = 10) transplantation between February 1990 and December 1991 were studied to learn the incidence and severity of acute rejection and the possible effects of various immunosuppressive protocols on this rejection.[13] Acute rejection was less common (2.1 *vs.* 3.1 episodes/patient) after transplantation in those 30 candidates who received RATG for the first 5 postoperative days *versus* the 28 who were maintained on cyclosporine, azathioprine, and prednisone alone ($p < 0.05$); however, no patient escaped at least one episode. Patients given cyclosporine received more 3-day courses of methylprednisolone ($p < 0.02$) than those given RATG (2.5 *vs.* 1.7 courses). Although no disadvantage in terms of infectious morbidity was noted in the RATG group, no obvious advantage was noted in survival (85% at 12 months), grade of rejection, or airway flows. The most common histopathologic grades were mild (A2) and moderate (A3); the average grade was A2.3.

Our center's experience with the new immunosuppres-

sant, FK 506, is evolving. The drug was recently successfully used in a number of children with fewer late episodes of rejection and improved results.[14] To further evaluate the potential benefit of FK 506 over cyclosporine-based immunosuppression, we randomly assigned the two drugs to 57 recipients between October 1991 and December 1992. Six months' graft survival was significantly better in the FK group (86%) as compared to the cyclosporine-treated group (69%) ($p < 0.05$). Late graft failures in the cyclosporine-treated group were due to unexplained diffuse alveolar damage,[2] bacterial pneumonia,[3] *Aspergillus* pneumonia,[1] and lymphoproliferative disease.[1] Acute rejection contributed to graft failure in two instances. Late graft failures in the FK group were due to primary CMV pneumonitis,[1] adenoviral pneumonia,[2] and *Pseudomonas* pneumonia.[1] For 90 patient days, there were significantly fewer episodes of acute rejection in the FK group (1.6) as compared to the cyclosporine-treated group (2.2) ($p < 0.05$, unpaired t test). While only 1 recipient in the 29 treated with cyclosporine remained free from acute rejection within 90 days, 5 of 28 (21%) of the FK-treated patients remained free from acute rejection during this same interval ($p < 0.05$). The control of the allogenic response did not appear to be at a consequence of increased risk of bacterial infection because the cyclosporine group had 0.7 episodes per 90 patient days and the FK group had 0.4 episodes. The prevalence of cytomegaloviral and fungal infections was similar in both groups.

Bronchiolitis Obliterans

Chronic rejection was defined by histologic evidence of bronchiolitis obliterans in the absence of infection and was associated clinically with dyspnea and/or cough, sometimes productive or purulent sputum, and a progressive restrictive and obstructive defect of pulmonary function.[15] It has been the most important complication that affects recipients after 100 days. It occurred with a prevalence of 37% (40 of 107 recipients at risk) and was responsible for 46% of the late deaths (Fig. 4, bottom). Thirteen of 40 patients with obliterative bronchiolitis have died of the complication. Obliterative bronchiolitis occurred at a median of 336 days, but had been diagnosed as early as 60 and as late as 2058 days. Since the use of surveillance bronchoscopy with transbronchial biopsy was introduced in 1988, only 30% of recipients have had symptoms or abnormalities of pulmonary function before diagnosis of obliterative bronchiolitis. In the very early experience, five recipients were treated without augmented immunosuppression, and all experienced progressive variable decline in pulmonary function that terminated in respiratory failure and death. Three of these recipients also experienced bronchiectasis with *Pseudomonas aeruginosa.* Subsequently, treatment with augmented immunosuppression by way of three daily doses of 1 g, methylprednisolone, or 5 days of RATG resulted in long-lasting remission in 30% of recipients, no response in another 16%, or remission followed by eventual relapse in 48%. Overall, 75% of recipients responded with stabilization or improvement in their symptoms, pulmonary function, or lung histology. Each relapse was associated with decline in pulmonary function that did not return to baseline.

DISCUSSION

As with most forms of new therapies, results are expected to improve with experience. In pulmonary transplantation, improvement derives from increased understanding of appropriate candidates, operative choices, surgical techniques, and postoperative surveillance for and treatment of infection and rejection. In this report we have compared an initial 9-year experience with 130 procedures and a 61% actuarial 1-year survival rate to a 70% survival rate obtained in the recent group undergoing 115 procedures. While the improvement is gratifying, it has been limited to (1) the inclusion of a large number of high-risk recipients; (2) the effort to explore single and double lung transplantation for those patients with advanced pulmonary hypertension and right heart failure; (3) operative advances that have not always paced technical challenges associated with Eisenmenger's syndrome and intrathoracic inflammatory scarring residue of septic lung diseases; and (4) imperfect immunosuppression that imperfectly controls the allogenic response and host defenses against infection.

Between June 1990 and July 1992, 266 of 588 (45%) patients with end-stage disease who were referred to us for consideration of lung transplantation were accepted as candidates for the procedure. Of those, 51 (19%) died awaiting a donor at an average of 56 days from listing, 74 (38%) underwent transplantation at an average of 8 months after listing, and 141 (53%) currently await donor lungs. Generally, all candidates were well within accepted guidelines for end-stage diseases and most were mortally ill. Arterial blood gases and spirometric values did not discriminate those who died awaiting transplantation from those who underwent transplantation or those who remain on the list. All patients required continuous oxygen, and most were home- or hospital-bound. The 27 with obstructive lung disease and 24 with cystic fibrosis had low forced expiratory volumes that ranged between 17% and 24% of normal. The majority of candidates with cystic fibrosis displayed a high degree of antibiotic resistance. The poor outcomes noted in this report after transplantation for patients with cystic fibrosis and antibiotic-resistant *Pseudomonas* species or

Pseudomonas cepacia have also been observed by others. Of the 22 recipients with PPH or Eisenmenger's syndrome, the right ventricular ejection fraction averaged 28% and the cardiac index was below 2.2 L/min/m^2 in all.

Review of recent survival suggests an advantage for patients with obstructive lung disease over the other major groups, including primary pulmonary hypertension, Eisenmenger syndrome, and cystic fibrosis. Patients with emphysema generally had good cardiac function, an absence of infection, an uncomplicated operation without the need for cardiopulmonary bypass, and, if single lung was employed, a safety net of the remaining lung in case of acute allograft dysfunction or infection. While overall our 10-year experience demonstrated a poorer outcome associated with heart-lung transplantation, recently there has been near equal survival of heart-lung (72%), double lung (63%), and single lung (77%) patients. We strongly believe that survival is linked more to the indication for transplantation and the severity of illness than to the type of procedure required. The superior results in children without cystic fibrosis who were treated by the various forms of pulmonary transplantation are notable.

The extreme limit in the number of heart-lung donors available forced us to increasingly adopt double and single lung transplantation as alternatives to heart-lung transplantation for candidates with pulmonary hypertension with and without significant cor pulmonale. While we continue to be unsure of the most appropriate procedure for patients with severe pulmonary hypertension, we have been pleased with the early results of the alternative use of single and double lungs and have been struck by the improvement in right ventricular function that follows the significant reduction in pulmonary artery pressure after either form of lung transplantation alone.[16] The impact of these forms of therapy on our candidate waiting list has resulted in a drop from 60 of 85 candidates awaiting heart-lung transplantation in May 1990 to only 16 of 136 in December 1992. We remain unsure whether double or single lung should be reserved for only those candidates with pulmonary hypertension or also the other nonseptic parenchymal diseases as well. Clearly, if a single lung can provide similar short- and long-term results, it will predominate as more patients will be served by this organ-conserving operation. Heart-lung transplantation will probably be reserved for those candidates with either severe left ventricular dysfunction, coronary artery disease, or complex congenital heart defects beyond the scope of reasonable correction associated with lung transplantation.

Familiarly with heart-lung transplantation and the adoption of technical advantages, including the use of a double-lumen endotracheal tube, bilateral anterior thoracotomy with transverse sternotomy, and extramediastinal anastomosis of the bronchi, has resulted in fewer operative deaths from bleeding. Additionally, we have, through improved exposure, reduced the incidence of injury to phrenic, vagus, or recurrent laryngeal nerves in all forms of pulmonary transplantation.

An evaluation of the early causes of death after pulmonary transplantation shows that while bleeding, allograft dysfunction, and infection are less common, the latter continues to be responsible for the majority of losses (35%). The transplanted lung is unique among all other organs in its communication by airways to the nosocomial environment. It is subject to seeding from continuing infection of the recipient's airways and sinuses. This is especially common in patients with cystic fibrosis. Early infection is more likely in the setting of a need for prolonged mechanical ventilation in the cachectic, weakened recipient, the imperfect nature of *ex vivo* lung preservation that virtually assures some allograft reperfusion injury, and a reduced host response in the allogenic and immunosuppressed environment. One wonders whether further advances in infection control can be obtained. Clearly, selection of less ill recipients, avoidance of those with pan antibiotic-resistant organisms, and development of improved donor screening and preservation techniques will result in improved outcomes. Broadening of our perioperative antibiotic coverage from cefamandole in the early days to ceftazidine and clindamycin plus an appropriate aminoglycoside when gram-negative organisms are present has helped to reduce the incidence of early pneumonia from 50% (25 of 50 at-risk recipients) to 9% (7 of 78). Airway cultures of *Candida* now prompt 4 weeks of fluconozol and cultures of *Aspergillus* prompt amphotericin (0.5 to 2 g). Finally, the prophylactic use of ganciclovir has reduced the prevalence of cytomegaloviral infection from 71% (22 of 31 at risk) to 16% (7 of 44). Late infection occurring after 100 days has almost always occurred only in the setting of chronic rejection and diseased airways. Thus, attempts at limiting losses from late infection must be focused on the prevention and therapy of obliterative bronchiolitis.

We and others have found that acute rejection after single lung, double lung, and heart-lung transplantation is common and should be anticipated. Recipients of lung transplants virtually never escape an early episode and require frequent surveillance by transbronchial biopsy, examination of chest radiograph, and evaluation for arterial desaturation; they often show clinical signs, including fever, shortness of breath, and generalized fatigue. We were surprised to find a high incidence of asymptomatic patients who had histologic evidence of acute rejection and obliterative bronchiolitis. We believe that given the short-term and possible long-term adverse effects of undiagnosed rejection, which include sudden dysfunc-

tion and progressive obliterative bronchiolitis, aggressive therapy of a positive biopsy is justified. While RATG did not affect the short-term outcome, it was associated with fewer episodes of acute rejection. Whether this will translate into a reduced risk of chronic rejection in these individuals is speculative. But, based upon our experience with cardiac transplantation, prophylactic forms of cytolytic therapy have not influenced the ultimate appearance in the graft of coronary artery disease, which is also believed to be a form of chronic rejection. We are encouraged by the early results with FK 506 in children[14] and in the preliminary randomized trial in adults that suggests a reduced incidence of acute rejection and increased survival.

While early complications have been reduced in recent experience, the hazard rates of the causes of death suggest an ongoing late risk of death from chronic rejection and associated infection (Fig. 5). Clearly, these problems limit the benefit of pulmonary transplantation and have become the most important challenge in the endeavor. Nothing is more devastating than to care for a recipient of a lung transplant who for a short period has benefitted greatly by the transplant but who once again becomes breathless and disabled by lung disease. Retransplantation for obliterative bronchiolitis has not been successful to date because of a high operative risk and significant chance of early recurrence of obliterative bronchiolitis.[17] The problem of chronic rejection will not be easily managed, but improvements will probably come from better surveillance, earlier treatment with more effective immunosuppressants, and a concentrated effort to learn the basic pathophysiology of the allogenic process.

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Discussion

DR. NORMAN E. SHUMWAY (Palo Alto, California): I enjoyed this paper tremendously, as always, from the Pittsburgh Transplant Group.

In the early days of lung transplantation, the results were so miserable from single lung transplants that we thought the answer at that time—this was back in the late 1970s—would be to do the heart-lung block. That way we could monitor the events of rejection in the lung by cardiac biopsy, thinking that since it's the same genetic background that we would have that information through cardiac biopsy.

Well, this turned out not to be the case because there is an asynchronicity of rejection of the heart and the lungs. So, it's necessary now, obviously, to perform a biopsy on the lung as well as on the heart. I would ask Bart how they monitor pulmonary rejection? Are they relying more on x-ray or actual biopsy?

Now, we have a couple of philosophical differences. One of them is that we think patients with cystic fibrosis and pulmonary hypertension, whether it be Eisenmenger or a primary pulmonary hypertension, should be treated by heart-lung transplantation, our best treatment.

But, of course, the problem comes in the tremendous donor shortage and the fact that today there are 160 hospitals in the United States alone trying to do cardiac transplantation. Many of their patients are labeled Status 1 so that if a heart-lung block becomes available, we're forced essentially to do the sequential bilateral lung transplants and give the heart to some other more