Improved results of lung transplantation for patients with cystic fibrosis

Patients with cystic fibrosis pose particular challenges for lung transplant surgeons. Earlier reports from North American centers suggested that patients with cystic fibrosis were at greater risk for heart-lung or isolated lung transplantation than other patients with end-stage pulmonary disease. During a 3½ year period, 44 patients with end-stage lung disease resulting from cystic fibrosis underwent double lung transplantation at this institution. During the same interval, 18 patients with cystic fibrosis died while waiting for lung transplantation. The ages of the recipients ranged from 8 to 45 years, and mean forced expiratory volume in 1 second was 21% predicted. Seven patients had *Pseudomonas cepacia* bacteria before transplantation. Bilateral sequential implantation with omentopexy was used in all patients. There were no operative deaths, although two patients required urgent retransplantation because of graft failure. Cardiopulmonary bypass was necessary in six procedures in five patients and was associated with an increased blood transfusion requirement, longer postoperative ventilation, and longer hospital stay. Actuarial survival was 85% at 1 year and 67% at 2 years. Infection was the most common cause of death within 6 months of transplantation (*Pseudomonas cepacia* pneumonia was the cause of death in two patients), and bronchiolitis obliterans was the most common cause of death after 6 months. Actuarial freedom from development of clinically significant bronchiolitis obliterans was 59% at 2 years. Results of pulmonary function tests improved substantially in survivors, with forced expiratory volume in 1 second averaging 78% predicted 2 years after transplantation. Double lung transplantation can be accomplished with acceptable morbidity and mortality in patients with cystic fibrosis. (J THORAC CARDIOVASC SURG 1995;109:224-35)

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Cystic fibrosis (CF) is the most common lethal genetic disease of the white population. Although the disease affects several organ systems, more than 95% of affected individuals die of pulmonary insufficiency.[1] It is estimated that up to 400 patients with CF die annually in the United States alone.[2]

The past decade saw remarkable advances in understanding the pathophysiology of CF, including identification of the chloride channel abnormality[3] and the responsible gene[4] and creation of a transgenic mouse with CF.[5] Expected survival has increased from 10 years in the 1960s to 28 years in 1990.[2] Promising new therapies that have become available for the treatment of patients with CF—for example, ameloride,[6] uridine triphosphate[7] and deoxyribonuclease[8]—may enhance chances of pro-

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longed survival. There is speculation that "gene therapy" may provide the ultimate cure for patients with CF.[9] Nevertheless, thousands of patients with CF will likely die of the devastating effects of severe bronchiectasis caused by inspissated infected pulmonary secretions. For these patients, replacement of infected, irreversibly damaged lungs by transplantation may offer improved length of survival and quality of life.

Initial reports of heart-lung transplant efforts for patients with CF in North America were discouraging.[10] Increasing experience and modifications of technique have led to improved prospects for patients with CF undergoing lung transplantation. In this report, we summarize the results of double lung transplantation at one institution in patients with CF with end-stage lung disease.

Patients and methods

Since January 1990, 81 patients have undergone 85 isolated lung transplant procedures at the University of North Carolina Hospitals. The 44 patients with CF from this group form the basis of this report.

Patient selection. Selection criteria for pulmonary transplantation have been published previously[11]; the criteria for patients with CF are as follows:

Age less than 50 years
Life expectancy 18 to 24 months
No significant renal or hepatic disease
No evidence of malignancy for more than 5 years
Ambulatory and able to participate in rehabilitation program
Ability to understand and comply with a complex medical regimen
Psychologic stability
Previous pleural procedures acceptable
No panresistant organisms in sputum

Data with respect to pulmonary function, pulmonary cultures, history of hospitalization, and relevant psychosocial history were obtained from referring physicians. Prospective candidates were evaluated to identify other organ system dysfunction—especially renal, cardiac, or hepatic dysfunction—that might preclude a successful outcome of transplantation.[12] Candidates were evaluated by a team consisting of psychologists, social workers, and physicians experienced in the management of patients with CF. Thereafter, a consensus was reached regarding the suitability of candidates. In general, in the absence of contraindications, transplantation was offered to patients with a life expectancy of less than 24 months without a transplant. Patients with confirmed panresistant organisms are currently not considered candidates.

Estimating life expectancy without transplantation is difficult, but certain objective parameters such as hypercarbia, increasing oxygen requirement, and forced expiratory volume in 1 second of less than 30% predicted are associated with a poor prognosis in CF.[13] Other concerns include the requirement for more frequent hospitalizations and the loss of functional capacity. In an earlier analysis of our CF referrals, 41 of 57 referred candidates (72%) were found to be acceptable for transplantation; four of these chose not to be listed.[14] During the period in which these 44 patients have undergone transplantation, 18 additional patients with CF died waiting for lung transplantation.

Listed candidates are required to relocate close to our transplant center and to participate in a preoperative program of pulmonary rehabilitation, consisting of monitored, graded aerobic exercise. Ideally, listed patients participate in the rehabilitation program for 2 to 3 months before transplantation.

Transplantation technique. Lungs were retrieved from donors through a median sternotomy. After infusion of 500 μg prostaglandin E_1 (Prostin, Upjohn, Kalamazoo, Mich.) into the pulmonary artery, donor lungs were flushed with modified Euro-Collins solution (80 ml/kg). All recipients received preoperative and perioperative antibiotic prophylaxis tailored to the most recent sputum cultures and sensitivities, continued for a mean of 10 days after the operation.

The transplantation technique first outlined by Pasque and associates,[15] described in more detail elsewhere,[16] has been used for patients with CF. The operation is performed through an anterior bilateral thoracosternotomy, or "clamshell" incision, made through the fourth or fifth intercostal space, with sequential removal and implantation of both lungs. A preoperative quantitative radionuclide perfusion scan identifies the lung with the least perfusion, which is removed first. Cardiopulmonary bypass (CPB) is deliberately avoided in general, but it is used when necessitated by inadequate ventilation or right heart failure. Bronchial omentopexy is performed, with omentum mobilized through a midline laparotomy, based on the gastroepiploic artery, delivered into the chest through a substernal tunnel, then split to wrap both anastomoses. We have found bronchial healing to be superior with end-to-end anastomosis and omentopexy,[17] compared with the telescoping technique first described by Calhoon and colleagues.[18]

Strategies to minimize contamination of the pleural space have been devised. Use of a double-lumen endotracheal tube reduces the risk of cross-contamination between a native CF lung and the newly implanted graft. During explantation of the native lung, the bronchus is clamped distal to the line of division to reduce egress of purulent secretions, and the open airway and empty pleural space are irrigated with povidone-iodine (Betadine) solution after pneumonectomy before implantation. A bronchoscope is used after transplantation to aspirate any purulent secretions.

Patients were not excluded because of prior thoracic surgical procedures. One patient had a previous lobectomy for hemoptysis; five had pleurodesis (one pleurectomy, one talc poudrage, and three mechanical abrasions) for pneumothorax; and three had prior chest tubes (one for an empyema).

Immunosuppression. Postoperative immunosuppression consisted of cyclosporine (Cyclosporin A; Sandoz, Basel, Switzerland), begun intravenously in the operating room;

Table I. *Demographics of CF recipients and donors*

Variable	*Recipient*	*Donor*
Age (yr)	23.2 ± 1.2 (8-45)	26.9 ± 2.0 (4-52)
Weight (kg)	42.8 ± 1.5 (20-68)	63.4 ± 2.6 (20-95)
Height (cm)	160 ± 2.2 (114-185)	168 ± 2.6 (112-200)
Sex (M/F)	20/24	23/21
Weight for height (%)	76 ± 1.6 (58-106)	

Donor/recipient weight ratio (mean) 1.5 ± 0.05 (0.9 to 2.1).

azathioprine (2 mg/kg); and antilymphocyte globulin, initially University of Minnesota antilymphoblast globulin, 15 mg/kg per day, and more recently Atgam (Upjohn).[19] Systemic steroids were generally withheld until 2 weeks after transplantation, when prednisone was introduced at a dose of 0.5 mg/kg per day. Systemic steroids were reduced gradually to a dose of 15 mg every other day in adults 1 year after transplantation. Because oral cyclosporine is poorly absorbed in patients with CF, ketoconazole was routinely administered concomitantly to reduce metabolism of cyclosporine.[20]

Episodes of acute rejection were treated with bolus intravenous methylprednisolone (15 mg/kg for 1 to 2 days, reduced to 7.5 mg/kg, total therapy 3 days). Rejection was diagnosed on the basis of transbronchial lung biopsy, according to published criteria,[21] or on clinical grounds, such as pyrexia or altered gas exchange, with or without pulmonary infiltrate on chest radiograph, in the absence of pulmonary infection.[19] All patients except one were treated for rejection within the first 2 weeks.

Intraoperative management. General anesthesia for recipients was induced with fentanyl and maintained with isoflurane. Intubation with a left-sided double-lumen tube was routine for adults and large children. Recipients judged to be too small for a double-lumen tube were managed with a single-lumen endotracheal tube and bronchus-blocking balloons. Airway maintenance with suction is imperative throughout the operation, and occasionally bronchoscopy for airway toilet is necessary to allow for adequate ventilation. Obstruction of the left upper lobe orifice with the distal balloon of the double-lumen tube is a frequent occurrence, resulting in hypoxemia.

Postoperative management. Patients were extubated when pH could be maintained in the normal range and oxygenation was adequate. Bronchoscopy, transbronchial biopsy, and bronchoalveolar lavage were performed at 1 week, 3 weeks, and every 3 months for the first year after the operation and when indicated clinically to investigate a radiographic abnormality, altered gas exchange, or unexplained fever. Bronchoscopy was delayed during the first week after transplantation if treatment for rejection had been initiated on clinical grounds.

After discharge from the hospital, patients continued to participate in a rehabilitative program of monitored aerobic exercise, which afforded an opportunity for close outpatient follow-up. The duration of participation in postoperative rehabilitation depended on progress; patients were advised to expect to remain in the geographic area of the transplant center for 2 months after hospital discharge.

Lung function and other measurements. Percent forced vital capacity (FVC) and percent FEV_1 were calculated after measurement of FVC and FEV_1 by means of standard nomograms. Six-minute walk tests (the distance walked in 6 minutes) were performed when patients were seen for evaluation and at intervals before and after the operation. Percent ideal body weight was calculated for each recipient.[22]

Statistics. Numeric results are expressed as mean ± standard error of the mean. Comparisons were made with Student's *t* test or analysis of variance where appropriate.

Results

Since October 1990, 44 patients have undergone double lung transplantation for CF at our institution. The demographics of the transplantation cohort are summarized in Table I. Two male patients survived brief periods of ventilatory support before being evaluated and listed. The condition of four other patients deteriorated while they were awaiting transplantation after being listed, necessitating ventilator support for 7 to 19 days before transplantation. These patients underwent successful transplantation during ventilator support.[23] Eighteen listed patients have died awaiting transplantation. Waiting time has increased in each year of the program (Fig. 1).

Organisms identified in respiratory tract cultures in patients before transplantation were representative of the spectrum of organisms seen in patients with CF. All *Pseudomonas* species were resistant to several antibiotics, but none were determined to be pan-resistant in vitro at the time of evaluation for transplantation and listing. Eight patients harbored *Pseudomonas cepacia,* three had nontuberculous *Mycobacterium,* and *Aspergillus* was recovered from 24 patients.

Operative and postoperative data are presented in Table II. Because the lungs are implanted sequentially, ischemic times are presented for each lung. The additional ischemic time for the second lung represents the time for extraction of the remaining native lung and implantation of the second graft.

CPB was required on six occasions, usually because of inability to oxygenate associated with refractory respiratory acidosis. CPB was associated with a larger blood transfusion requirement and with our only two cases of renal failure necessitating temporary dialysis after the operation. In two instances, substantial hemorrhage was related to lung abscesses of the upper lobe that involved the

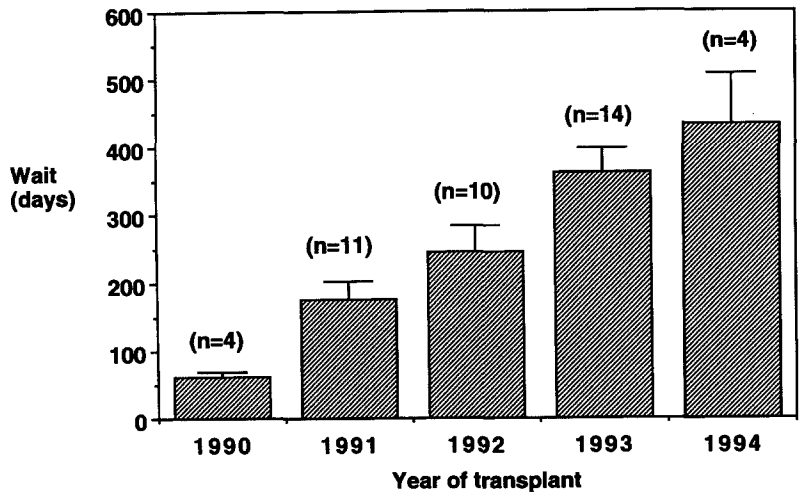

Fig. 1. Waiting time after listing for patients with CF at University of North Carolina Hospitals, by year. The number of transplantations performed in each calendar year is shown in *parentheses.* One patient was excluded in 1991 because he was transferred from a heart-lung list with a 3-year wait accumulated.

chest wall to such an extent that the pleural space was totally obliterated; both patients were unable to tolerate one-lung anesthesia, necessitating institution of CPB. CPB was also associated with a longer requirement for postoperative ventilation, with a mean of 6 ± 2.5 days in patients requiring CPB (excluding the patient requiring urgent retransplantation), compared with a mean of 1.8 ± 0.26 days in patients who did not require CPB ($p < 0.0005$, t test).

Because of the size discrepancy between donors and CF recipients (see Table I), size reduction procedures were used after transplantation in nine patients. These procedures consisted of right middle lobectomy or nonanatomic resections with a TA 90 stapler (United States Surgical Corporation, Auto Suture Company Division, Norwalk, Conn.), excising the lingula, the apical portion of the lung, or a portion of the lung base posteriorly. Analysis of the impact of this pneumoreduction strategy has confirmed that the reduced sized lungs more closely conformed to predicted recipient total lung capacity and had no adverse impact on measurable spirometric volumes after transplantation.[24]

All patients have survived the operation to be discharged from the hospital ambulatory and without supplementary oxygen. Two patients required retransplantation for acute graft failure on postoperative days 8 and 13, respectively. Both survived after protracted hospital courses. Actuarial survival was 86% at 1 year and 67% at 2 years (Fig. 2). Deaths have arbitrarily been classified as early (within 6 months of transplantation) and late (beyond 6 months), and the causes are outlined in Table III.

Table II. *Perioperative data*

Ischemic time (min)	
First lung	311 ± 9.4
Second lung	470 ± 13
Blood use in operating room (units packed cells)	
With CPB (n = 6)	
Mean	21.5 ± 1.9
Range	15-28
Without CPB (n = 38)	
Mean	6.05 ± 0.6*
Range	1-17
Duration of ventilation (days)	
Mean	2.2 ± 0.4
Range	1-13
Median	1
Hospital stay (days)	
Mean	28 ± 3.3
Range	14-129
Median	21

*$p < 0.0001$.

For purposes of discussion, complications have been grouped as surgical, medical, and infectious. Postoperative complications (exclusive of infection) are given in Table IV. Unilateral phrenic nerve palsy was observed in three patients early in the series. This is thought to be related to the use of rigid metal retractors on the mediastinum to improve exposure of the hilum. Since abandoning the use of metal retractors and using only a hand instead, we have

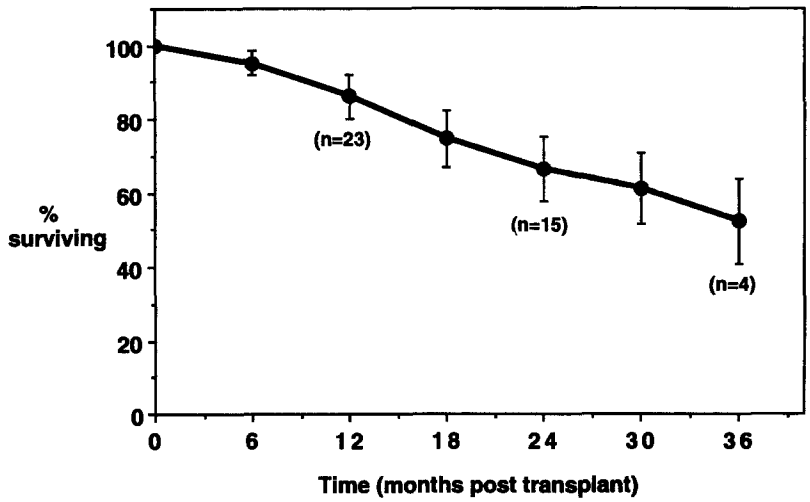

Fig. 2. Actuarial survival (Kaplan-Meier) of patients with CF having double lung transplantation. (Data ± 95% confidence limits.)

Table III. *Causes of death*

	No.
Early (<6 mo after transplantation)	
Pneumonia (*Pseudomonas cepacia*)	2
Unexplained CNS death	1
Late (>6 mo after transplantation)	
Obliterative bronchiolitis	6*
CMV pneumonia	1
Lymphoma	1
Suicide	1

*Noncompliance contributed to two of these deaths.

Table IV. *Complications*

	No.
Surgical	
Graft failure necessitating retransplantation	2
Unilateral phrenic nerve paresis	3
Bronchial dehiscence	
Contained (no air leak)	2
With air leak	1
Airway stricture (stent)	1
Wound problems	
Sternal wound infection	2
Sternal dehiscence necessitating reclosure	1
Ventral hernia*	1
Axillary vein thrombosis	6
Gastrointestinal complications	
Gastric atony	7
with bezoar	6
Bowel obstruction/meconium ileus equivalent	4
Cholelithiasis after transplantation	2
Choledocholithiasis after transplantation	1
Pericarditis (staphylococcal)	1
Medical	
Renal failure (temporary dialysis)	2
CNS event	
Cerebrovascular accident	1
Unknown high intracranial pressure	1
Seizures, new	12
Ascites, related to portal hypertension*	1
"Difficult" diabetes	8
Posttransplantation lymphoproliferative disorder	2
Osteoporosis resulting in spontaneous fractures	1

*Related complications in the same patient.

seen only one additional case of phrenic nerve paresis. We believe that the retraction used to expose both pleural spaces likely places the phrenic nerves under some traction, setting the stage for neuropraxia if additional retraction is applied to the pericardium.

Bronchial healing has not been a cause of major morbidity in this subgroup of patients. Three instances of partial bronchial disruption have been observed bronchoscopically. Two of these were contained, but a bronchopleural fistula developed in one patient, necessitating percutaneous drainage of a cavity. All bronchi healed without stenosis. One stricture developed in the bronchus intermedius of the oldest recipient in the series, distal to a well-healed anastomosis. This was treated with insertion of a Dumon silicone rubber stent (Bryan Corp., Woburn, Mass.).[25] Healing of the skin incisions, and in particular the transverse sternotomy, has been problematic in only a small number of patients. One patient had a ventral hernia associated with postoperative portal hypertension and ascites, and one other patient required rewiring of the sternotomy for early breakdown. Two or three sternal wires were used for closure in adult patients; heavy braided suture was used in pediatric patients.

Twelve patients have had grand mal seizures after transplantation. In three instances, cerebral abnormalities were identified on computed tomographic scan after the first seizure and were believed to be contributory: one patient had an embolic event; one had an ischemic focus thought to be related to high preoperative carbon dioxide tension despite mechanical ventilation; and one patient had several postoperative watershed infarcts, probably resulting from intraoperative hypotension and blood loss related to an abscess of the upper lobe involving the chest wall. In several patients the seizures were usually associated with elevated systemic blood pressure. One seizure disorder was unmasked during a posttransplantation bronchoscopic study when a large dose of intraairway lidocaine had been administered. Two other cases became apparent after treatment of rejection with bolus steroids. The complication of posttransplantation epilepsy not associated with structurally identifiable brain lesions in our patients having lung transplantation has been seen only in lung recipients with CF and is particularly troublesome to treat, because phenytoin enhances cyclosporine metabolism, further complicating the dosing of this drug in these patients.

Infectious complications are summarized in Table V and are reported, both by number of patients and number of courses of therapy, as events necessitating antibiotic therapy. Infection of the graft was common. Bronchitis, defined as airway purulence without radiographic pneumonitis or consolidation, necessitating therapy is a frequent problem in patients with obliterative bronchiolitis. Pneumonia (diagnosed clinically or radiographically) was treated in 18 patients on 42 occasions. Two patients have died of *Pseudomonas cepacia* pneumonia, which became apparent several weeks to months after transplantation. One patient had persistent fever, and a *Pseudomonas cepacia* mediastinal abscess was found 2 months after transplantation. Despite percutaneous drainage, a necrotizing pneumonia of the right upper lobe developed. This was surgically resected as a sleeve right upper lobectomy. This airway anastomosis healed, but multiple pulmonary abscesses and bilateral necrotizing *Pseudomonas cepacia* pneumonia developed, resulting in the patient's death 3½ months after transplantation. *Pseudomonas cepacia* has been a recognized cause of increased morbidity after double lung transplantation for CF at other centers.[26]

A clinical diagnosis of sinusitis was made in 17 patients on 29 occasions. Five patients have had surgical sinus drainage, all after transplantation. Bacteremia has been documented in five patients, proved to be "line related" in two.

Table V. *Infectious complications: indications for posttransplantation treatment with antibiotics*

Indication	*Patients (n)*	*Courses (n)*
Bronchitis	27	60
Pneumonia	18	42
Sinusitis	17	29
Bacteremia	10	11
Fever, no organism or site	7	8
Nontuberculous *Mycobacteria*	2	2
Fungal or yeast infection	6	8
CMV disease	27	44
Varicella	2	2
Herpes simplex virus	1	1

Cytomegalovirus (CMV) disease is a common occurrence. Twenty-seven patients have been treated on 44 occasions with gancyclovir for CMV disease. Only three patients had serious CMV pneumonia necessitating supplemental oxygen; one of these died without benefit of mechanical ventilation. We abandoned a policy of matching CMV-negative recipients to CMV-negative donors after the sixth patient in the series. We have not found gancyclovir prophylaxis to be efficacious in lung transplant recipients.[27]

Despite the purulent nature of the end-stage lung disease in these patients, only two instances of empyema have occurred, one in a patient with *Pseudomonas cepacia.* There have been two sternal wound infections. One of them, which occurred in the aforementioned patient, was managed with drainage and reclosure and appeared to be healing at the time of death from *Pseudomonas cepacia* pneumonia. The other infection was drained and is currently a small draining sinus.

A more thorough analysis of the infectious complications after transplantation among our patients with CF has been published elsewhere.[28] Surprisingly, infectious complications in CF recipients of lung transplants are no more prevalent than those found among recipients with other diagnoses of end-stage lung disease.

Bronchiolitis obliterans is a major cause of late death in this series. To date, 15 patients have had clinical or pathologic[21] evidence of obliterative bronchiolitis. Six of the 12 have died as a result of obliterative bronchiolitis, one underwent retransplantation but died 3 months later of CMV pneumonia, and one patient is awaiting retrans-

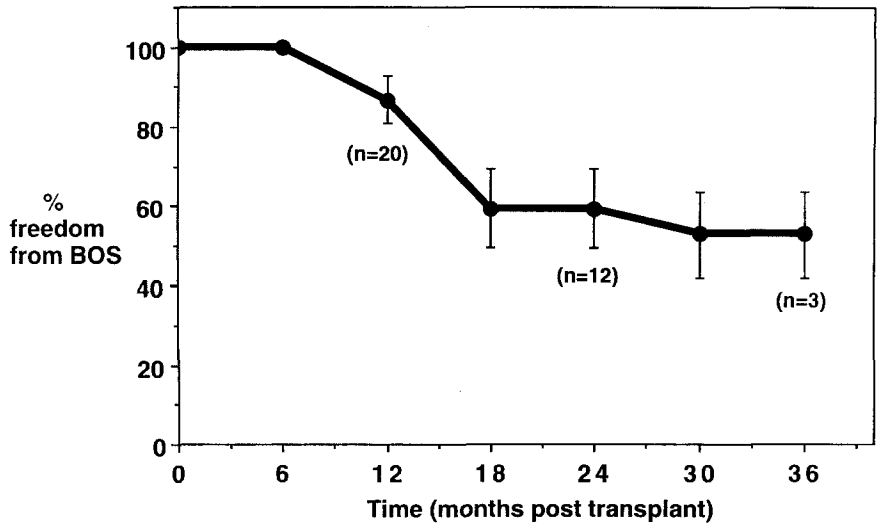

Fig. 3. Actuarial freedom from bronchiolitis obliterans syndrome *(BOS)* (grades I, II, and III), calculated according to the Kaplan-Meier method. Patients dying of causes other than bronchiolitis obliterans were treated as "withdrawn" for purposes of this analysis. (Data ± 95% confidence limits.)

plantation. For purposes of reporting, bronchiolitis obliterans syndrome has been classified according to clinical criteria.[29] Five of six patients who had grade III bronchiolitis obliterans syndrome either died or were listed for retransplantation. Two of three patients with grade II and one of two with grade I bronchiolitis obliterans syndrome died; noncompliance with medication contributed to the development of bronchiolitis obliterans syndrome in two patients who died. Four patients have shown evidence of obliterative bronchiolitis on transbronchial biopsy specimens with little or no decrement in FEV_1; thus there are four patients with grade "zero-B" bronchiolitis obliterans syndrome. The actuarial freedom from development of clinically significant bronchiolitis obliterans syndrome (grades I to III) among our lung transplant recipients with CF is depicted in Fig. 3. No patients have had clinical evidence of bronchiolitis obliterans within 6 months of transplantation, but the risk of bronchiolitis obliterans syndrome developing increases dramatically after 6 months.

Postoperative FVC and FEV_1 (expressed as percent predicted) are depicted in Fig. 4. Despite the inclusion of patients with known bronchiolitis obliterans, the postoperative spirometric data are encouraging and have been associated with improvement in functional status. Six-minute walk data from patients who underwent transplantation are depicted in Fig. 5. Within 3 months of transplantation, 80% of recipients have had New York class I functional status.

Discussion

The past decade has seen unsurpassed advances in the field of pulmonary transplantation. Since the first heart-lung transplantation, performed by Reitz and associates[30] in 1981, and the first successful single lung transplantation in 1983,[31] more than 2000 lung or heart-lung transplant procedures have been reported to the Registry of The International Society of Heart and Lung Transplantation.[32]

Patients with CF pose vexing problems to the transplant surgeon. These include the systemic effects of chronic disease; the nutritional deficiency related to chronic infection and intestinal malabsorption, with the concomitant difficulty of erratic absorption of lipid-soluble cyclosporine; and colonization of the airway and sinuses with antibiotic-resistant strains of gram-negative organisms. Chronic pulmonary infection often results in the formation of dense pleural adhesions. These can also be the consequence of recurrent pneumothoraces, a common problem in patients with CF, resulting in thoracostomy tube drainage, pleurodesis, pleurectomy, or pulmonary resection. Episodes of hemoptysis may also have led to pulmonary resection or bronchial artery embolization. Hepatic dysfunction related to CF is common, renal insufficiency may be

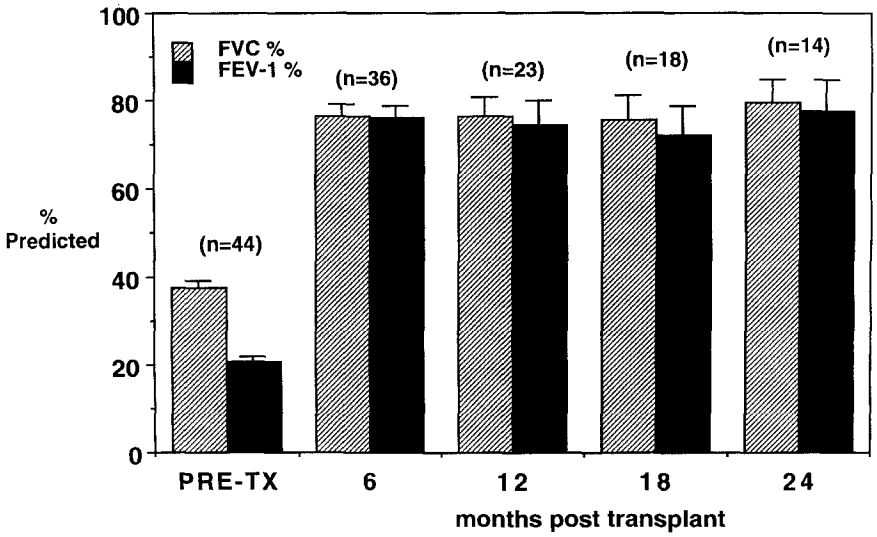

Fig. 4. FVC and FEV_1, expressed as percent predicted for CF lung transplant recipients at time of evaluation for transplantation *(EVAL)* and at intervals after transplantation. (Mean ± standard error of the mean.)

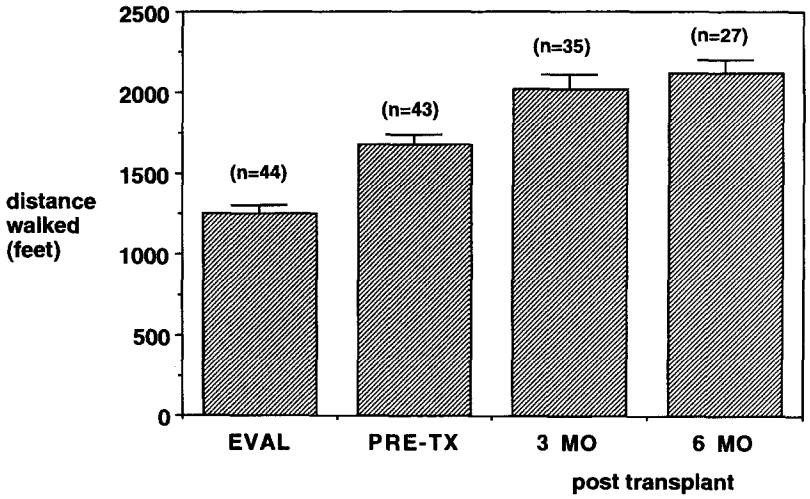

Fig. 5. Distance walked in 6 minutes at time of evaluation for transplantation *(EVAL)*, after rehabilitation *(PRE-TX)*, and at intervals after transplantation. Improvement in performance was significant at each interval depicted ($p < 0.05$ by paired Student's t test).

the sequela of aminoglycoside therapy of *Pseudomonas* infections, and glucose intolerance may be the result of endocrine pancreatic insufficiency. All of these problems may increase the risk of transplantation in these individuals.

In other respects, patients with CF are potentially ideal candidates for lung transplantation. They are frequently young, with life-threatening disease confined to one organ system. Even before the genetic defect was established, it was apparent that the pulmonary epithelial abnormality of CF, evidenced by an altered potential difference,[3] was not manifested in the epithelium of heart-lung grafts in patients with CF.[33] This observation provided some assurance that the pulmonary abnormalities observed in patients with CF were unlikely to recur after transplantation.

These problems have been responsible for a cautious approach to lung transplantation in patients with CF. In 1990, Yacoub and colleagues[34] from

Harefield reported 27 heart-lung transplants in patients with CF over a 4-year period, with only four operative deaths and 1- and 2-year actuarial survivals of 78% and 72%, respectively. Papworth Hospital, Cambridge, reported results of heart-lung transplantation in 32 patients with CF over a 5-year period, with five early deaths and a 1-year actuarial survival of 73%.[35] Heart-lung transplantation was initially applied to CF with discouraging results in North America, with a 42% 1-year actuarial survival reported from several centers surveyed.[10]

Noirclerc and coworkers[36] were the first to report on double lung transplantation for CF using a bibronchial anastomotic technique through a median sternotomy with CPB. The next step in the evolution of the surgical technique was the "clamshell" incision and the sequential lung transplantation technique described by Pasque and colleagues.[15] The University of Toronto outlined its 3-year experience of double lung transplants in 17 patients with CF, one having the "old" en bloc technique with a tracheal anastomosis, two with bibronchial anastomoses, and the most recent 14 operated on by the sequential technique, with actuarial survivals at 3 and 12 months of 66% and 58%, respectively.[37] Much of the mortality encountered in this series was related to infection with *Pseudomonas cepacia.*

Shennib and associates[38] reported a 64% actuarial survival at 1 year in patients with CF undergoing double lung transplantation from two centers, one on either side of the Atlantic. Despite the potential for increased risk in this patient population, there is evidence that patients with CF have the same perioperative and postoperative mortality as other patients having lung transplantation, because actuarial survival reported to The International Society for Heart and Lung Transplant Registry is similar for patients with CF and other recipients of double lung transplants.[32] More recently, an updated report from Papworth Hospital has made the same observation.[39]

Apart from the instances of documented cerebral damage (three cases), we have no explanation for the increased tendency for epilepsy to develop in our patients. Both cyclosporine and steroids can lower the seizure threshold; cyclosporine levels have occasionally been high, and our routine use of ketoconazole to reduce cyclosporine metabolism may play a role.

Although all prospective candidates are assessed by a clinical psychologist before transplantation, noncompliance has contributed to two deaths, and one other patient committed suicide despite good pulmonary function 8 months after transplantation. Undoubtedly, the stress associated with a chronic life-threatening illness contributes to morbidity and mortality in this patient population.

Despite the morbidity associated with pulmonary transplantation in patients with CF, we remain gratified by the well-documented improved pulmonary function and quality of life of the recipients, and we are pleased with the survival of this group of patients. We attribute this success to several factors. First, a team of surgeons, physicians, nurses, physiotherapists, and other health care workers has been assembled in an institution with considerable experience in the management of patients with CF. We believe that a program of pulmonary rehabilitation is essential to prepare these debilitated patients for pulmonary transplantation. Our aggressive approach to early postoperative extubation and ambulation is possible, we believe, only because of the rehabilitation program.

Second, the evolution of the surgical technique of double lung transplantation has been instrumental in allowing for this degree of operative survival. The bilateral thoracotomy incision has dramatically improved intrathoracic exposure, rendering extraction of lungs from patients with CF safer than previous approaches through a sternotomy. Pleural adhesions in these patients are frequently numerous and vascular, and they can be divided, for the most part, under direct vision. A second advantage of the procedure, we believe, is the ability to avoid CPB in most cases, which in our experience has substantially reduced transfusion requirements and lung injury, shown by reduced postoperative ventilation requirement in patients in whom CPB was avoided. This has recently been documented by Aeba and colleagues.[40] We believe that these factors make isolated lung transplantation the procedure of choice for patients with CF, rather than the so-called "domino procedure," wherein the recipient of a heart-lung graft provides a donor heart to another recipient.[34] It is irrational to replace the heart of a patient with CF unless there is a concomitant severe degree of biventricular cardiac failure.

Three pressing problems facing lung transplantation today are the scarcity of suitable pulmonary donors, early graft dysfunction, and the development of bronchiolitis obliterans, leading to organ failure in many recipients. The organ donor shortage may ultimately be solved by the use of xe-

nografts, although current understanding of immunology precludes this. The use of bilobar transplants from living related donors has been proposed, and a small experience exists with this strategy for patients with CF,[41] but this option may be impractical for many adults with CF. The use of circulation-arrested cadavers may increase the donor pool and may be a particularly attractive option for lung transplantation programs.[42]

Bronchiolitis obliterans is a poorly understood process that is prevalent after heart-lung or isolated lung transplantation. Evidence is mounting that the process is an immunologic one, but there is a plethora of predisposing risk factors, including viral infection. Response to augmented immunosuppression is inconsistent.[43] Retransplantation for patients with end-stage bronchiolitis obliterans is controversial, because the outcome of retransplantation is poor for lung transplant recipients.[44]

This report documents that isolated lung transplantation can be undertaken with acceptable mortality in patients with CF, despite the potential for increased risks in these patients.

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Discussion

Dr. Alec Patterson *(St. Louis, Mo.).* Dr. Egan, you and your colleagues are to be congratulated for a remarkable achievement to conduct that number of transplants in a group of patients with CF. They are the most difficult group of patients that we are asked to see for transplantation. We reported a smaller experience several years ago from Toronto with much less impressive results than you have described.

You mentioned that 18 patients died on the waiting list. What percentage of your waiting list do these 18 patients represent? Do you have any sense of how long the wait for a donor is, both for those who died and those who underwent the transplant operation?

I would appreciate your thoughts about the use of alternate strategies to get these patients to transplantation. What are your comments about lobar transplantation? Perhaps Dr. Starnes might want to comment on this specific subject. Pulmonary bipartition is another interesting strategy. I would also appreciate your comments as to whether these patients should be stratified on the waiting list so as to achieve transplantation more often in those patients who have the highest mortality rate.

Dr. Egan. The contribution that you and the group from the University of Toronto made for transplantation in patients with CF is widely recognized. I think it is fair to say that the group in Toronto was cursed with a population of patients in whom *Pseudomonas cepacia* was very prevalent. This is a nasty organism that is difficult to treat. In fact, much of the morbidity and mortality in the series that you allude to from Toronto was related to problems with *Pseudomonas cepacia*.

As I mentioned, 18 patients have died on our waiting list. The difference between patients who died and patients who were able to survive long enough to undergo transplantation was that the patients who died waiting were generally sicker at the time of referral. Their FEV_1 was significantly lower than that of the transplanted patients, who had an average FEV_1 of 20% predicted at the time of their transplantation.

Lobar transplantation is an interesting solution to the problem of death on the waiting list. It will be applicable to some patients, but size discrepancies, blood incompatibilities, and other potential problems are going to limit its applicability to all patients with CF. I am intrigued by the notion of splitting a lung and servicing a patient with two half lungs, and I think that is one strategy that merits further study.

It is a shame that in this country we are not identifying all potential donors. In particular, we are not identifying and distributing all lungs from donors that become identified. I think that the United Network for Organ Sharing should look very seriously at the amount of time that patients have to wait for lungs and what is happening to lungs that are not being transplanted.

Finally, we are attempting to address the donor shortage in our laboratory. We believe that it may be possible to retrieve lungs from circulation-arrested cadavers for transplantation.

Dr. John R. Benfield *(Sacramento, Calif.).* Is it a correct recollection from your slides that the ischemic time for the second donor lung was unusually long? If that is a correct observation, would you comment on some of the factors that contribute to that? Do you think that may have contributed to your early graft failure?

Dr. Egan. We do not know the upper limit for ischemic time. The intent is to try to keep it as short as possible, but the extraction of these lungs can be very difficult. If the donor lungs arrive in the operating room before we are quite ready for them, that is, before we have done the dissection on both sides, we will transplant the side that we are ready to do and then extract the lung on the other side. This program has also developed a transplant fellowship, and we have a responsibility to train other surgeons in the surgical technique. That adds a little time to each transplant procedure. However, we have been fortunate that the long ischemic times have not translated into poor pulmonary function. In fact, one of the patients who required retransplantation had one of the shortest ischemic times of any of our patients.

Mr. Ali Rahman *(Manchester, England).* We do not see any need for using omentum, we had no problems at all with dehiscence, and we use bypass in all double lung transplants, which shortens the operating time. One of our biggest problems is that we are pressured by the chest physicians wanting us to operate on patients with CF. After our first few successes they moved the CF unit right to the doorstep of the surgical ward. Thus I would like to direct my questions to the selection process, because it is a problem. First, do you operate on patients with totally resistant *Pseudomonas cepacia?* Second, I noticed that many of your patients have *Aspergillus* infection after the operation. Third, do you ignore CMV compatibility because of the shortage of donors? I notice that you had 27 cases of CMV infection afterward.

Dr. Egan. The issue of pan-resistant *Pseudomonas* is difficult to deal with. Even though *Pseudomonas cepacia* may start out being susceptible, it frequently becomes pan-resistant. We have not listed patients who had pan-resistant *Pseudomonas,* and to my knowledge none of our patients has had pan-resistant *Pseudomonas* at the time of transplantation. On two occasions, however, the organism became pan-resistant after transplantation, and this was lethal in both instances.

We do see *Aspergillus* frequently in cultures before transplantation. I believe one of the reasons we have not had significant postoperative problems with *Aspergillus* or *Candida* is that we avoid systemic steroids in these patients for the first 2 weeks. Although there is some discussion about whether that is beneficial for airway healing, I think it does change the flora in the upper airway and may contribute to morbidity in other arenas.

With respect to CMV, we will cross CMV barriers because of the shortage of donors. Recently we stopped giving all patients 2 weeks of ganciclovir prophylaxis, because our data did not indicate that that conferred any benefit. We will, however, use ganciclovir prophylaxis in mismatched patients for 4 weeks and treat them with hyperimmune CMV globulin. That strategy has resulted in an incidence of CMV pneumonia and CMV disease that is high but that has been responsible for only one death so far.

Dr. Vaughn A. Starnes *(Los Angeles, Calif.).* To give some follow-up on the lobar alternative strategies that can be used successfully, we have performed transplantation in seven patients with CF, with early survival in all. The real issue in those patients is that we *do* use CPB because we have been concerned about all the cardiac output flowing through that one lobar segment while the other is being transplanted. This is the only modification of the existing transplant technique that I would suggest might be important. In addition, with the introduction of aprotinin, we have been able to significantly reduce our use of blood after the operation.