The Past, Present, and Future of Lung Transplantation

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BACKGROUND: The history of lung transplantation from the first human transplant performed in 1963 to the present is reviewed with particular focus on the added challenges because of the contaminated bronchus, exposure of the graft to airborne organisms, the poor blood supply to the bronchus, and the problem of reperfusion pulmonary edema.

METHODS: The technical aspects of single and double sequential lung transplantation are reviewed, as are the current indications for single, double sequential, and heart/lung transplantation. Criteria for lung transplant recipients, in addition to their primary disease are noted, as are absolute and relative contraindications. The standard criteria for donor selection are also reviewed.

RESULTS: The results of single, double sequential, and heart-lung transplantation over the past 10 years as reported by the International Society for Heart and Lung Transplantation Database are reviewed. In addition, the statistics of the lung and heart-lung transplantation program at the University of Colorado Health Sciences Center are reviewed, including the current immunosuppressive regimens and early and late monitoring for infection and rejection. This experience includes 3 early deaths in the first 53 patients for an operative mortality of 5.6%, with a 1-year actuarial survival of 90%.

CONCLUSIONS: During the past decade remarkable improvement in the result of single and double sequential lung transplantation have occurred. As 1-year, actuarial survival is now approaching 90% at some institutions. Living related lobar transplantation, new antirejection agents, chimerism, and xenograft transplantation are areas for continuing and future investigation. The shortage in donor organ supply continues to be a very significant factor in limiting human lung transplantation. Am J Surg. 1997;173:523-533. © 1997 by Excerpta Medica, Inc.

One of the first pioneers in developing lung transplantation was Dr. James Hardy of the University of Mississippi, who, on June 11, 1963, performed the first human single lung transplant. The recipient died on the 18th postoperative day from renal failure. Of considerable interest is the fact that there was no rejection seen at autopsy. This patient was treated with antilymphocyte serum, prednisone, and radiation therapy.

From 1963 to 1983, 40 lung transplants were performed with no long-term survivals except for Derom's report in 1971 of a patient who underwent a right lung transplant and lived for 10 months. However, this patient spent most of his postoperative period hospitalized and eventually died of pneumonia with chronic rejection. His immunotherapy was antilymphocyte serum, azathioprine, and prednisolone, 50 mg daily.

Dr. Frank Veith made many contributions to the development of lung transplantation beginning in 1969 and extending through 1983. During that time he developed techniques for pulmonary artery and pulmonary venous anastomoses and described the telescoping anastomosis that Dr. Trinkle and I in the late 1980s erroneously felt we had developed. In 1979, Veith made the extremely important finding of the effect of donor bronchial length on healing of the bronchial anastomosis, noting that the shorter the donor bronchus the better the healing. It is my personal opinion that this is the single-most important detail in performing a successful bronchial anastomosis. In 1983, he reported improved experimental results with lung transplantation using cyclosporine.

The credit, however, for the successful clinical application of lung transplantation must go to Dr. Joel Cooper, who performed his initial work while at the University of Toronto under Dr. Griffith Pearson, the teacher and program director of many outstanding general thoracic surgeons. In 1978, Dr. Cooper performed Toronto's first single lung transplant on a 19-year-old burn patient with smoke inhalation injury. The patient had been hospitalized for 5 months and was ventilator dependent. He died on the 17th postoperative day of a bronchial dehiscence. This patient was of extremely high risk but played an important role in the development of the Toronto transplant program. In...
1981 Cooper's group demonstrated that steroids decreased bronchial healing but that azathioprine and cyclosporine had a minimal effect on bronchial healing. In 1983, Dr. Cooper and his colleagues reported that immunosuppressive medications increased bronchial disruption and necrosis. In 1983, he reported on studies using the omental wrap in an experimental model with improved bronchial healing and neovascularization. In 1983, Cooper and his colleagues performed the landmark single lung transplant procedure on a patient who was the first long-term survivor. This was a right lung transplant using an omental wrap in a 58-year-old male with end-stage pulmonary fibrosis. He was treated postoperatively with azathioprine and cyclosporine with prednisone beginning 3 weeks postoperatively. From 1983 to 1985, the Toronto group reported on 7 single lung transplant procedures, 5 of which survived, thus providing the impetus for the clinical application for this procedure and its tremendous growth throughout the world.

The indications for lung transplantation were originally defined by the Toronto group as progressively disabling end-stage pulmonary fibrosis with a life expectancy of 12 to 18 months, the patient being on home oxygen but not ventilator-dependent, and not on steroids. At that time, it was thought that chronic obstructive pulmonary disease (COPD), pulmonary hypertension, and cystic fibrosis were contraindications to lung transplantation. In 1988, Mal and Andreassian successfully performed a single lung transplant for COPD. Shortly after that, in January 1989, without the knowledge of Andreassian's accomplishment, Dr. Trinkle, our San Antonio colleagues, and I performed the first successful single lung transplant in North America for COPD. Since then, COPD, including the alpha-antitrypsin group, has been the most common application of single lung transplantation. Dr. Trinkle's willingness to take on this group of patients as well as the pulmonary hypertension patients with single lung transplantation is typical of his innovative and aggressive approach in broadening the indications for lung transplantation.

INDICATIONS

Current indications for single lung transplantation include restrictive lung disease for which the original procedure was done, emphysema, pulmonary hypertension, and other nonseptic, end-stage pulmonary disease including restrictive lung disease secondary to connective tissue disorders. Indications for bilateral sequential lung transplantation include cystic fibrosis and patients in whom there is chronic infection with end-stage pulmonary failure including patients with bronchiectasis. Many centers would also prefer bilateral sequential lung transplantation for patients with primary and secondary pulmonary hypertension because it appears to decrease reperfusion pulmonary edema. This group includes patients with primary pulmonary hypertension (PPH) as well as those with noncomplex congenital heart disease with pulmonary hypertension, the latter undergoing correction of the heart defect at the time of transplantation, thus avoiding a heart/lung transplant. Emphysema patients with lung volumes so great that it would be very difficult to find a large enough single lung also may be selected for bilateral lung transplantation. Indications for heart/lung transplants are patients who have complex congenital heart defects that are not easily correctable with end-stage pulmonary hypertension.

The primary pulmonary hypertensive group is somewhat unique in that these patients tend to be young, and may decompensate quickly. The role of prostacyclin in buying time should be evaluated for each patient. Single, bilateral sequential, and heart/lung transplants are options for this group. These patients are the only group that uniformly require cardiopulmonary bypass. The advantages of single lung transplant in this group are that it conserves donor organs, it is technically more simple, it is very effective in decreasing pulmonary vascular resistance thereby improving the right ventricular ejection fraction, and gives good symptomatic relief. The disadvantages are that reperfusion pulmonary edema is frequently a major problem and can be fatal, 85% of the pulmonary blood flow goes to the transplanted lung creating a V/Q mismatch so that dysfunction of the transplanted organ is not well tolerated, and rejection is poorly tolerated for the same reason. The operative mortality is 26%, and the actuarial survival at 1 year is 66%. PPH patients are often young and therefore may be better served in the long run by two lungs. The advantages of bilateral sequential lung transplantation for this group of patients are that it offers even distribution of pulmonary flow to both lungs and therefore leads to less reperfusion edema and to easier perioperative management. In addition, acute or chronic rejection episodes are better tolerated with less V/Q mismatch. This procedure also reduces pulmonary vascular resistance and increases right ventricular ejection fraction very nicely. The advantage over heart/lung transplantation is the heart can be used for another recipient. The operative mortality for bilateral lung transplantation for PPH is approximately 10% and the 1-year actuarial survival is 77%, somewhat better than single lung transplantation. The disadvantages are that a bilateral sequential lung transplant is technically more difficult, requires longer cardiopulmonary bypass time, and uses two lungs per patient, thus depleting the already short supply of acceptable donor lungs. Heart/lung transplantation for PPH is also useful if there is left ventricular dysfunction or very severe right ventricular dysfunction with severe tricuspid regurgitation, or aneurysmal pulmonary arteries. The 1-year survival for this procedure is only 62%. The disadvantages of heart/lung transplantation are that it is technically more demanding, it uses a heart that could go to another recipient and carries a significant operative mortality of 21%. Finally, the dominant procedure can be used for this group of patients where a heart/lung transplant is performed but the recipient's heart is transplanted into another recipient. This heart would almost certainly have right ventricular conditioning so that it might function more adequately in a heart transplant recipient who has some increase in pulmonary vascular resistance. The disadvantage is that the domino heart may have some myocardial damage or tricuspid valve abnormality because of its exposure to increased pulmonary vascular resistance and might not tolerate the ischemic time involved with transplantation.

RECIPIENT CRITERIA

The ideal lung transplant recipient has disease confined to the lungs with no other major organ dysfunction or disease. The patient ordinarily should be under 65 years of age.
for a single lung transplant, under 60 for a bilateral sequential transplant, and under 50 for a heart/lung transplant. It is important that the patient be compliant with no significant drug or alcohol dependence history and be psychologically stable.

Contraindications for single, double sequential lung transplant, or a heart/lung transplant are multisystem disease other than lung, history of carcinoma or sarcoma with a possibility of recurrence, current infection, significant renal or hepatic dysfunction, cigarette smoking within 3 to 4 months, drug or alcohol abuse, psychiatric instability, and poor medical compliance. Bronchiectasis and chronic or recurrent pulmonary infection are contraindications for single lung transplantation and require double sequential lung transplantation.

Relative contraindications to lung transplantation are insulin-dependent diabetes mellitus, being outside of the above mentioned age criteria, the presence of significant coronary artery disease and/or left ventricular dysfunction (these patients would best be treated with heart/lung transplantation), long-term ventilation support, previous thoracic surgery, weights of greater than 20 mg per day or greater than 0.2 to 0.3 mg kg/day, hemodynamic instability, extreme cachexia, morbid obesity, advanced connective tissue disease associated with other organ dysfunction such as esophageal motility dysfunction or renal disease, and previous lung transplantation. These are relative contraindications however, and we have performed single lung transplants on patients with a history of coronary disease in whom there was no active ischemia.

**DONOR CRITERIA**

The standard criteria for donor selection are for the donor to have a partial pressure of oxygen (PO2) of greater than 300 mm Hg with ventilator settings of 100% fraction of inspired oxygen (FIO2), a positive end-expiratory pressure (PEEP) of 5 cm H2O, and a tidal volume of 12 cc per kilogram per minute. The chest x-ray should be clear, the sputum should be negative for fungus and preferably negative for gram-negative rods, there should be no purulent secretions, the age should be 60 or younger, HIV and hepatitis B and C antigens should be negative, and the donor should be on a ventilator for less than 1 week. The donor should have no history of lung disease including asthma, no history of cancer except for nonmelanomatous skin cancer, no history of "high risk" behavior, the circumference at the nipple line should be within 4 to 5 inches of the recipient's, there should be reasonable matching of the height/weight, vertical and horizontal lung dimensions (vertical dimensions no less than 75% of recipients), a less than 30-pack year smoking history, and no gross purulence from lobar or segmental orifices on bronchoscopy.

Over the past several years, because of the shortage of donor organs, there has been some liberalization of the criteria for accepting donor lungs. Age has been liberalized to many centers into the 60s, smoking history has been accepted up to 30- to 40-pack years, sputum Gram stain for gram-negatives are sometimes acceptable if the bronchoscopy does not show any active purulent secretions from the lobar and segmental orifices, patients with pulmonary contusion or a history of a traumatic pneumothorax are accepted if the contusion is not excessively large and if there is not a large active air leak. Small infiltrates on x-ray are not a definite contraindication if there is no gross purulence at bronchoscopy. Some patients with a unilateral pneumonia and a negative bronchoscopy on the opposite lung are acceptable. In addition, patients with atelectasis can often be improved by increasing the tidal volume in the operating room during the donor procurement. Occasionally lungs can be used in patients with a PO2 of less than 300 mm Hg if this is secondary to atelectasis or if there is contralateral lung dysfunction. In the latter situation if the pulmonary artery to the dysfunctional lung is clamped, the PO2 should rise above the minimum 300 mm Hg if the other lung is a satisfactory organ for transplantation. Size criteria has been liberalized somewhat, particularly when performing a bilateral sequential lung transplant, where smaller organs can be used. One must be cautious about any oversizing for a bilateral procedure because this could cause compression of the heart. Cytomegalovirus (CMV)-positive donor organs are now being transplanted into CMV-negative recipients at some centers because of the availability and effectiveness of ganciclovir and cytagam (CMV hyperimmune globulin); early results are encouraging, although at this point long-term results are not available. The use of donors who have suffered brain death on the basis of carbon monoxide or cyanide poisoning have been reported. This would appear to be acceptable if there is a period of time between the exposure to these agents and procurement with the demonstration of sustained good function of the lungs. The safe ischemic time for lungs has been increased to 8 to 9 hours because of improvement in donor preservation techniques.

The "high-risk" donor presents a difficult problem. The high-risk donor is generally identified as one who has a history of drug abuse, particularly intravenous drug abuse, promiscuous sexual behavior, a remote history of cancer, positive hepatitis serologies, but a negative HIV serology. There is some risk of transmitting hepatitis from these donors and also a small risk of transmitting HIV because the transplant could be during a window of time after infection with HIV but before the HIV test becomes positive. There is a role for the use of these high-risk donors for recipients who are critically ill who may not survive long enough for another donor to become available. In this instance, it would appear acceptable to fully inform the recipient and his/her family as to the fact that the donor is "high-risk" and what the potential chances are of contracting one of the above diseases.

It is the author's opinion that all donors should undergo a bronchoscopy to rule out the presence of pneumonia, acute bronchitis, and the presence of foreign bodies. In the process of bronchoscopy a mucus plug can be removed and by a combination of suctioning of mucus plugs and increasing the tidal volume one can expand atelectatic segments of the lung. This also allows the donor team to discriminate between acceptable and unacceptable donor lungs in an individual patient.

Shuhway and colleagues from the University of Minnesota have nicely demonstrated that there has been no detrimental effect on survival for lung transplantation because they have liberalized the criteria for organ donors, much as described above.
DONOR TECHNIQUE

The technique of lung procurement is relatively straightforward. A median sternotomy and a connecting midline laparotomy are performed. The heart is dissected out in the usual fashion for heart transplantation, the pleura are opened longitudinally posterior to the sternum and the pericardium is divided from anterior to posterior back to the hilum on both sides. Both lungs are carefully inspected, the inferior pulmonary ligament is taken down with the electrocautery, all pleural adhesions are incised, the proximal pulmonary arteries are dissected at their origin from the main pulmonary artery, the patient is heparinized with 30,000 units of heparin, either intravenously or into the opened longitudinally posterior to the sternum and the pericardium and pulmonary artery delivery is complete, the heart is excised and are ventilated by the anesthesiologist during the administration of cardioplegia and pulmonoplegia are administered with the right heart being vented through the inferior vena cava incision and the left heart being vented through the left atrial appendage incision (Figure 1A). Cold modified Euro-collins solution is infused at 0° to 4°C by a catheter in the pulmonary artery to a volume of 3 liters with gentle squeezing of the plastic bag. Simultaneously, ice slush saline is placed over the lungs in both pleural cavities. The lungs are ventilated by the anesthesiologist during the administration of the pulmonoplegia. Once the cardioplegia and pulmonoplegia delivery is complete, the heart is excised and in the process buttons of left atrium that include the entrance of the right pulmonary veins and the left pulmonary veins are created with a 5-mm to 10-mm cuff around the venous orifices. During removal of the heart the right and left pulmonary arteries are divided at their takeoff from the main pulmonary artery (Figure 1B). Following removal of the heart, the pulmonary arteries are dissected free from proximal to distal, and the pericardium and mediastinal structures around the hilum and the pulmonary arteries are divided sharply with great care not to injure the pulmonary veins as they enter the atrial cuff. The trachea is dissected free and the takeoff of the both the right and left main stem bronchi are dissected free but no dissection of the bronchi is performed distal to the takeoff from the carina. Three 4.8 staple lines are fired, one across the distal trachea, one at the proximal left main bronchus, and one at the proximal right main bronchus. This is done following insufflation of the lungs to 35 cm H₂O by the anesthesiologist who holds the lungs inflated at this point. Great care should be taken to be sure there is no atelectasis present in either lung before the firing of the staples. At this point, the trachea and bronchus are divided between the staple lines leaving the lungs fully inflated. The lungs are then removed from the pleural spaces, triple bagged in ice saline slush, and placed in a ice cooler for transport.

RECIPIENT TECHNIQUE

The technique for transplanting the lung into the recipient is as follows: For a single lung transplant, the patient is placed in a full lateral position and a posterior lateral thoracotomy incision is performed with the fourth intercostal space being entered for patients with restrictive pulmonary disease and the fifth intercostal space for those with obstructive pulmonary disease. The patient is ventilated through a left sided double lumen tube and the patient is monitored with radial artery and Swan-Ganz catheters. Great care is taken by the anesthesiologist to avoid “auto PEEP” in COPD patients, and also to restrict intravenous fluids. All blood products are CMV-negative and leukopore filtered. The recipient pulmonary artery is identified and dissected.
free proximally and distally. The pericardium is opened posterior to the phrenic nerve just anterior to the hilum and the incision is extended circumferentially around the hilum exposing the lateral atrial wall at the junction of the pulmonary veins. The main stern bronchos is identified and dissected free just proximal to the takeoff of the upper lobe bronchus. Care is taken not to dissect the more proximal portions of the bronchus where the bronchial anastomosis will be performed because this could impair the blood supply to the bronchus. Upon arrival of the donor organ the patient is heparinized with 100 units of Heparin/kg unless cardiopulmonary bypass is required, in which case the dose would be 300 units per kilogram. If cardiopulmonary bypass is required and it is a left-sided single lung transplant this would be done with femoral artery-femoral vein bypass. If right-sided, the inflow would be through the aorta and outflow from a dual stage atrial caval cannula. The lung to be removed is collapsed, an angled vascular clamp is placed on the proximal pulmonary artery and an U schild clamp is placed on the atrium to include the confluence of the pulmonary veins. The pulmonary artery is divided as far distally as possible just proximal to the lobar branches, the pulmonary veins are divided as close to the lung as possible and the main stem bronchus is divided one to two rings proximal to the takeoff of the upper lobe bronchus. The two pulmonary vein orifices in the recipient left atrium are then connected to form one orifice and one or two more cartilages are generally removed from the bronchus to be sure of a good blood supply. The donor lung is brought into the field, the staple line is excised from the donor bronchus to allow the lung to deflate to improve exposure, and the left atrial anastomosis is performed by anastomosing the cuff of the donor atrium to the cuff of the recipient atrium using a single 4-0 prolene suture beginning posteriorly and running around anteriorly (Figure 2A). The bronchial anastomosis is then performed. One of the most important aspects of this technique is to excise all donor cartilages down to just one or two cartilages proximal to the takeoff of the upper lobe bronchus, thus keeping the donor bronchus as short as possible because its blood supply will be totally dependent on pulmonary artery collaterals. This anastomosis is performed with 4-0 prolene sutures beginning initially with two corner sutures incorporating the cartilage just adjacent to the membranous portion of the bronchus. One of these sutures is tied and then run to the other corner and tied (Figure 2B). Following this, the anterior two thirds of the bronchus is anastomosed using interrupted figure of eight 4-0 prolene sutures encircling the cartilage and intussuscepting the donor bronchus into the recipient bronchus as shown in Figure 2C. The pulmonary artery anastomosis is performed with a single running 4-0 prolene running suture (Figure 2D).

A bilateral sequential lung transplant is formed through a bilateral thoracotomy (clamshell incision) going from one posterior axillary line to the other traversing the sternum with the chest being entered through the fourth intercostal space and the internal mammary artery and vein being secured with suture ligatures bilaterally. The patient is then tilted one side up and the same technique for a single lung transplant is performed first on one side, usually the right side, and then on the second side. The sequence is different if there is a major discrepancy in the lung function as measured by V/Q scan and in this situation the worst recipient lung would be removed and transplanted first.

Following completion of the lung transplantation and closure of the chest, the patient is placed back in the supine position, the double lumen tube is removed and is replaced with a single lumen tube and the patient is bronchoscoped to examine the anastomosis and to remove secretions from both the transplanted and non-transplanted lungs.

THE INTERNATIONAL EXPERIENCE

There has been a very significant increase in the performance of single lung transplantation from 1983 to 1993 as recorded in the International Society for Heart and Lung Transplantation Database, with over 500 single lung transplants having been performed in 1993 (Figure 3). The most common indication for single lung transplantation is emphysema (58%), including the alpha-antitrypsin group, with pulmonary fibrosis the second most common indication (17%). Survival has improved considerably over the past 6 years as noted in Figure 4, with 1-year actuarial survival at approximately 70% and 3-year at 55%, although in 1995 it is higher than this in most programs. The variation in survival according to diagnosis is noted in Figure 5, with the best results being in the emphysema patients and the worst in the patients with PPH patients and idiopathic pulmonary fibrosis (IPF). These differences are largely due to early mortality with the slopes of the curves being very similar after 1 month.

There has also been a marked increase in the performance of double lung transplantation since 1990 with the advent of the bilateral sequential technique, over 300 having been performed in 1993. The largest group of bilateral lung transplants are in the cystic fibrosis group (38%), followed by emphysema (29%). Nine percent of patients with PPH have received a bilateral lung transplant, although this is more commonly employed today. When the survival of bilateral lung transplantation according to the disease for which transplantation was performed is analyzed, the highest mortality was in the cystic fibrosis group.

The survival for heart/lung transplantation has been quite similar over 12 years with very slight improvement in early survival, the 3-year survival being about 50%. Survival curves for transplantation for PPH reveal an advantage for the bilateral lung transplantation as compared with heart/lung and early mortality for single lung (Figure 6). However, beyond 2 months postoperatively the slopes of the survival curves are relatively similar.

THE UNIVERSITY OF COLORADO EXPERIENCE

The lung transplantation program at the University of Colorado Health Sciences Center was established in the Fall of 1991 with the first transplant being performed in February 1992. This program has been successful because of the unselfish contributions of a multidisciplinary group that includes four surgeons, seven anesthesiologists, three pulmonologists, a nurse coordinator, a pulmonary rehabilitation therapist, a psychiatrist, a social worker, a physical therapist, a financial services specialist, and many other medical personnel. Without the broad participation of all
of these specialties as well as highly trained operating room, surgical intensive care, and transplant ward nurses, a lung transplant program cannot be successful. In addition to these specialties, the infectious disease service, the general surgical services, critical care services, radiology, and respiratory therapy have been very helpful.

The immunosuppressive regimen employed preoperatively is cyclosporine, 5 mg/kg orally, and Imuran, 2 mg/kg po. Intraoperatively the patient is given 500 mg of methylprednisolone immediately before reperfusion. Postoperatively patients are maintained on cyclosporine, 3 mg to 7 mg per hour intravenously for 2 days and then converted to 5 mg/kg orally twice a day or dosed as necessary to maintain a cyclosporine blood level at approximately 450 by the Abbott TDX Monitor. They are given daily doses of Imuran, 2 mg/kg; methylprednisolone, 125 mg every 12 hours for 6 doses, and 1 mg/kg per day the first week, and 0.75 mg/kg per day, 0.5 mg/kg per day, and 0.25 mg/kg per day. Most of our patients are then weaned down to a daily prednisone dose of 7.5 mg to 10 mg daily.

In addition, the patients are given ganciclovir, 5 mg/kg twice a day for 14 days and then 5 mg/kg once a day for another 2 to 4 weeks. They are also given CMV hyperimmune globulin 150 mg/kg on postoperative day 1 and 100 mg/kg on postoperative days 14 and 28. In addition, they receive nystatin, bacitracin, acyclovir, following the ganciclovir, H2 blockers, antacids, colace, magnesium, Lasix, potassium supplements, and frequently calcium channel blockers.

Postoperatively the patients are closely monitored for infection and rejection. Unfortunately many of the signs for rejection and infection are the same, with infection frequently presenting with purulent sputum, a localized infiltrate, fever, leukocytosis, oxygen desaturation, and cough. Rejection can also present with infiltrates, although these are more apt to be diffuse rather than localized, pleural effusions, leukocytosis, oxygen desaturation, and cough. The diagnosis is generally made with a combination of bronchoscopy, bronchoalveolar lavage, rapid CMV culture, and transbronchial biopsy.

Figure 2. A. This drawing illustrates the left atrial anastomosis, which is performed with a single 4-0 prolene suture. LA = recipient left atrium, PV = donor pulmonary veins, PA = pulmonary artery, LMB = left main bronchus. Single lung transplantation: alternative indications and techniques. B. The technique of the bronchial anastomosis is illustrated (A) with the two 4-0 prolene sutures being placed at the junction of the bronchial cartilage with the membranous portion of the bronchus on either side, (B) the membranous portion of the bronchus approximated by running one of these sutures to the other and tying it, (C) the interrupted figure of eight 4-0 prolene sutures encircle the bronchial cartilage, and (D) then telescoping the donor bronchus into the recipient bronchus. C. The illustration shows the completion of the insertion of the transplanted lung with a running 4-0 prolene pulmonary arterial anastomosis. (Reprinted with permission from Galhoon et al. J Thorac Cardiovasc Surg. 1991;101:816–825.)
From February 1992 through April 1995, 53 patients have undergone lung transplantation at the University of Colorado Health Sciences Center, 43 of whom had single lung transplantation, 9 bilateral sequential lung transplantation, and 1 heart/lung transplant. There were 3 early deaths (within 30 days or in hospital), and 5 late deaths. All received intraoperative methylprednisolone, none had an omental wrap, and the average length of stay was 17 days, excluding 2 outliers, with the shortest at 8 days and the longest at 145 days. In addition, our program performs approximately 25 adult and 25 pediatric heart transplants per year and 2 lung transplants have now been performed in the pediatric age group at Denver Children’s Hospital. The shortest waiting time for a lung transplant has been 2 days and the longest 608 days, with a mean of 215 days. Twenty-five of our patients have been female and 28 have been male. The Table lists the underlying disease for which the transplant was performed with the type of transplant and the result. Figure 7 demonstrates the actuarial survival curve for our single, double sequential, and heart/lung transplant program through March 1995.

Considerable symptomatic and physiologic improvement has been demonstrated, as shown in Figure 8, showing the total lung capacity before and after single lung transplantation in patients with restrictive lung disease and in Figure 9 with improvement in FEV1 in the single lung transplant group for obstructive pulmonary disease, and the 6-minute walk test for both groups following single lung transplantation (Figure 10). We have tried to oversize the trans-
planted lung in the restrictive patients and have attempted to transplant lungs within 75% of the size of emphysema patients.

Heart/lung transplantation represents a particularly challenging problem and is most commonly performed for patients with complex or incorrectable congenital heart defects who develop Eisenmenger's syndrome. Our only heart/lung transplant patient is a 19-year old female with a single ventricle and Eisenmenger's syndrome who has done very nicely.

**CURRENT CHALLENGES**

There are still several problems, however, that need to be worked out before lung transplantation will offer consistent and long-term relief of symptoms and longevity for the vast majority of patients. The problem of chronic rejection, as manifested by obliterative bronchiolitis continues to be a major concern. The Barnes Hospital group reported their experience with bronchiolitis obliterans reviewing 187 lung transplant patients surviving 3 months or longer whose procedures were performed between 1988 and 1994. They defined bronchiolitis obliterans syndrome as patients having a forced expiratory volume in 1 second (FEV1) of less...
than 80% of baseline and/or having histologic confirmation. Thirty-nine percent of their patients met these criteria, 49% by a declining FEV₁, 10% by histology alone, and 1% by both. The Pittsburgh experience reported by Paradis²¹ found that the time to occurrence of bronchiolitis obliterans after lung transplantation was a mean of 434 days and median of 322 days with a range of 60 to 2,058 days. Although there is no known absolute prevention for bronchiolitis obliterans, it is felt that aggressive prophylaxis for CMV is important and that in patients who have repeated episodes of rejection switching from cyclosporine to FK506 may be helpful. Probably most important is the early diagnosis of rejection episodes. This can be facilitated by aggressive use of home pulse oximetry, where the patients check their resting and exercise O₂ saturations daily and also with graded exercise with oximetry every several months. If rejection, either acute or chronic, is suspected, it is important to perform a bronchoscopic examination with bronchoalveolar lavage with routine, fungal, and viral cultures and transbronchial biopsy. Our general regimen is to treat patients with ganciclovir while awaiting the results of the cultures and biopsies. In the absence of infection we will usually treat the patient for rejection even in the absence of biopsy confirmation of rejection. The rejection regimen of the University of Colorado and many other institutions is to first treat with high-dose solumedrol with an oral prednisone taper. If this fails after a couple of courses of rejection then we proceed to the use of Atgam and if the patient returns with rejection again we would go to OKT³. If the patient has further episodes of rejection at this point we would switch from cyclosporine to FK506.

Another problem that occurs less frequently but can be devastating is post-transplant lymphoproliferative disorder. This entity occurs in approximately 5% of lung transplant patients and is initially treated by decreasing the immunosuppressive drugs, and if this is unsuccessful by adding chemotherapy.²³

Another challenging question in lung transplantation is whether or not to retransplant patients who develop either early graft failure or chronic rejection as manifested by bronchiolitis obliterans. There is a marked difference in the survival between first time lung transplants and reoperative lung transplants, with 1-year survival of approximately 40% for retransplant as opposed to 70-80% for a first time transplant. It is encouraging however, that in the past 3 years the results of retransplantation have significantly improved with the 1-year survival being slightly better than 50%.²⁴,²⁵ Retransplantation presents several ethical considerations, because most transplant surgeons bond very closely with their transplant patients but at the same time have an obligation to patients on the waiting list who have not yet had the opportunity to receive a transplant. Is it ethically correct to deplete the already limited supply of donor lungs even further by using them for retransplantation, knowing that the results of retransplantation represent at least a 20% to 25% lower chance of survival than first time transplants? Most studies indicate that retransplantation may be a reasonable procedure for relatively young patients who are carefully selected, who have initially done well, and late in their course develop chronic rejection as manifested by bronchiolitis obliterans.

**RECENT ACCOMPLISHMENTS**

Cohen, Starnes and associates have very ably demonstrated the efficacy of using living related donors for certain groups of patients, most notably, patients with cystic fibrosis where they have reported on 7 recipients receiving bilateral lungs from 14 living related donors most recently using the right lower lobe from one donor and the left lower lobe from the other donor.²⁶ There have been no donor deaths or complications except for prolonged airleaks in three of the donors, and they were during a period when the right middle lobe was being used as well as the right lower lobe. With removal of one of the lower lobes there has been an average decrease in donor forced vital capacity (FVC) of 17% to 18% and a decrease in FEV₁ of 17% to 20%. There have been no deaths in the cystic recipient group of living related transplants although there have been a few deaths in the infant and pediatric group that were transplanted for other reasons.²⁷ It would appear that the risk to the donor is minimal. Living related transplantation can offer earlier transplantation for patients who are at high risk on the waiting list, there is the potential for better organ compatibility, it expands the donor supply, and it is a continuation of a tradition of living related organ donation that has been long established for kidney transplantation and used occasionally for liver transplantation. Because of this, it would appear to be justifiable in carefully selected high risk patients on study protocols at selected sites.

Lung preservation techniques are now capable of preserving lung for up to 8 hours of cold ischemia, utilizing cold modified Eurocollins pulmonoplegia and intravenous PGE₁ to the donor. There is currently ongoing investigation regarding the use of antioxidant agents, leukocyte depletion, nitric oxide, and cytokine manipulation. In addition, there is continued investigation in improving immunosuppressive drugs. Cyclosporine G (Neoral), a new microemulsion form of cyclosporine is being used as well as FK506 (Prograf). The latter inhibits interleukin-2 synthesis, similar to cyclosporine, but it may be more potent. Mycophenolate mofetil (Cellcept) is being investigated for thoracic organ transplantation. This agent inhibits DNA and glycoprotein synthesis and in clinical trials in renal transplants decreased rejection.
and graft loss as compared to cyclosporine A and Azathioprine. Rapamycin, which blocks interleukin-2 lymphocyte proliferation is also being investigated. Monoclonal antibodies directed at the alpha-beta chain of T-cell receptors are being evaluated as are antibodies to CD4. Total lymphoid irradiation, photopheresis and genetic manipulation are also under investigation.  

**POTENTIAL FUTURE ADVANCES**

Starzl has a major interest and has performed many studies investigating chimerism, which is a natural occurring event after organ transplantation, human leukocyte antigen (HLA) incompatible bone marrow or donor-specific blood transfusion. He has found that recipients of cadaveric kidneys, livers, hearts, and lungs who are given donor bone marrow at the time of their transplant develop chimerism and that in FK506-prednisone-treated patients there is trend toward donor specific nonreactivity and increasing survival.  

There is considerable interest in the development of xenograft transplantation. Up to now this has been limited by the development of hyperacute rejection secondary to preformed antibodies from the recipient. Concordant xenografts (those that are phylogenetically closely related to humans) are limited by donor availability and the potential for transmission of infections. For this reason, discordant xenografts, such as pigs, have received intensive investigation. They have the advantage of being plentiful and come from animals that are already used in the human food chain. The disadvantage is that hyperacute rejection is still a problem and therefore there is much investigation needed regarding genetic manipulation of these animals to make them more similar to humans and to decrease the incidence of hyperacute rejection.  

**THE DONOR SHORTAGE**

Organ donor supply remains the principle limiting factor in human lung transplantation. In 1993, there were 656 lung transplants performed but there were 1,288 lung transplants on the waiting list and 60 heart/lung transplants performed with 206 patients on the waiting list. Thus, there is a 2:1 demand/supply ratio for lung transplants and over 3:1 for heart/lung transplants. For this reason, many patients die while on the waiting list, making it imperative for all of us in the medical community to continue our educational efforts in stressing the importance of organ donation to the public, while improving organ preservation and distribution, and expanding our criteria for acceptable donor organs and at the same time improving outcomes.

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**REFERENCES**