Review

Lung Transplantation

Lynn T. Tanoue

Yale University School of Medicine 333 Cedar Street New Haven, CT 06510, USA

Abstract. Advances in solid organ transplantation over the last several decades have made human lung transplantation a realistic possibility for selected patients with end-stage lung disease. A review of clinical indications, proper patient selection, and long-term management is presented. Infection and rejection continue to represent 2 major areas of posttransplantation complications and merit particular attention.

Key words: Lung Transplantation.

Over the past several decades, human lung transplantation has gone from being strictly experimental to being a realistic treatment option for some patients with end-stage lung disease. Lung transplantation was first attempted in dogs by Demikhov in Russia in the 1940s [4]. Further studies in dogs showed that transplantation was technically feasible, but raised concern that pulmonary denervation would alter respiratory patterns and lead to potential respiratory failure. Later studies in nonhuman primates showed that pulmonary denervation could be tolerated with minimal changes in respiratory and ventilatory pattern [15, 35]. These experiments led to the first attempt at single lung transplantation in humans by Hardy in 1963 [16]. The procedure was done in a 58-year-old man with recurrent pulmonary infections and complete left lung atelectasis due to a left main stem bronchus carcinoma. The patient died from progressive renal insufficiency on the 18th postoperative day, but at autopsy the transplanted lung showed no evidence of rejection. Over the subsequent 20 years, lung transplantation was attempted in a number of patients without long-term success [50, 53]. Only 1 recipient lived beyond the first few weeks, surviving for 10 months, most of that time confined to hospital and eventually dying from rejection, respiratory failure, and shock [8]. In 1968, the first human heart–lung

transplantation was performed by Cooley in a 2-month-old child, who survived for only 14 hr [3].

Throughout the 1970s and 1980s, progress in the laboratory and in transplantation of other solid organs made lung transplantation more feasible. The pioneering efforts in cardiac transplantation at Stanford University and other centers led to better methods of detecting rejection by endomyocardial biopsy and to major advances in immunosuppressive therapy to control rejection. The development of antithymocyte globulin and the recognition of the immunosuppressive effect of cyclosporin A were major breakthroughs [1, 22, 36]. In 1981, the first successful heart–lung transplantation was performed at Stanford in a young woman with primary pulmonary hypertension [40]. Heart–lung transplantation has since been used successfully in patients with primary pulmonary hypertension, Eisenmenger's syndrome, and in selected patients with end-stage lung disease and right ventricular failure.

The successes with cardiac and heart-lung transplantation renewed interest in single lung transplantation, which has several advantages over combined heart–lung transplantation in the patient for whom a single lung is adequate. In unilateral transplantation, premature coronary artery disease and the need to monitor for cardiac rejection are precluded, and cardiopulmonary bypass is usually not necessary during the surgery, thereby avoiding the problems associated with heparin therapy and prolonged periods of bypass. In addition, the donor lungs and heart can be transplanted individually, maximizing the use of the donated organs [50].

Studies of the early attempts at unilateral lung transplantation showed that dehiscence of the bronchial anastomosis contributed to the death of all transplant recipients who survived beyond the first 2 weeks [4]. This occurs because the procedure does not re-establish the bronchial arterial circulation, leaving the anastomosis without an oxygenated blood supply [33, 48]. The transplanted lung is unique among transplanted solid organs in this deficiency. Two developments from experimental transplantation in animals helped to resolve this problem. A technique of bronchial omentopexy was devised to facilitate revascularization of the bronchial mucosa [9, 27, 34]. The omentum is passed into the mediastinum, brought to the hilum, and wrapped around the bronchial anastomosis [11]. An intercostal flap or a pedicle of pericardial fat can be used in patients in whom omentopexy is unfeasible. These procedures to revascularize and protect the anastomosis, however, are not always necessary for successful transplantation. The other, and perhaps more important, breakthrough was the recognition of the adverse effects of perioperative corticosteroid therapy on the viability of the bronchial anastomosis. The Toronto Lung Transplant Group showed that such therapy contributed significantly to anastomotic dehiscence, whereas therapy with other immunosuppressive agents, such as azathioprine, did not [13, 28, 50]. This finding is critical because many patients with end-stage lung disease are treated with corticosteroids in attempts to alleviate symptoms and halt progression of disease. Since the pre- and perioperative corticosteroid therapy has been avoided, the severe complications of dehiscence have largely been eliminated, although the competence of the anastomosis remains a vital concern.

Table 1. Indications for lung transplantation

Single lung transplantation
  Pulmonary Fibrosis
    Idiopathic
    Familial
    Toxic exposure
  Chronic obstructive pulmonary disease
    α_1-Antitrypsin deficiency
    Other
  Sarcoidosis
  Eosinophilic granuloma
  Lymphangioleiomyomatosis
  Bronchiolitis obliterans
  Primary pulmonary hypertension (with adequate right ventricular function)
  Eisenmenger's syndrome (with correctable congenital cardiac lesion)
Bilateral lung transplantation
  Cystic fibrosis
  Bronchiectasis
  Primary pulmonary hypertension (with adequate right ventricular function)

As a result of these advances, the Toronto Lung Transplant Group performed the first successful single lung transplantation in 1983 in a 58-year-old man with idiopathic pulmonary fibrosis [50]. Despite 2 early episodes of rejection, this patient was discharged from the hospital 6 weeks after undergoing transplantation, and returned to work several months later. He survived for $6\frac{1}{2}$ years before dying from renal failure. The Toronto Group and others have continued to refine lung transplantation, expanding the surgical procedure to include double lung transplantation and bilateral sequential single lung transplantation [2, 14, 37, 49]. Since 1983, the number of transplants done per year has risen dramatically, and by 1991 more than 500 such procedures had been performed [24].

Indications for Lung Transplantation

Lung transplantation was originally done only in patients with end-stage pulmonary fibrosis [4, 14]. These patients were ideal candidates because they usually do not have chronic pulmonary infection; the poor compliance and high vascular resistance of their remaining native lung results in ventilation–perfusion imbalance favoring the transplanted lung; their native lung is not prone to hyperinflation, which might mechanically compromise the transplanted lung. Because of success with these patients, lung transplantation is now used in patients with other forms of chronic end-stage lung disease. Current indications for single and bilateral lung transplantation are shown in Table 1.

Patients with chronic obstructive pulmonary disease (COPD) now constitute a large number of referrals for single lung transplantation [10, 51]. Such

patients were not initially thought to be candidates because the high compliance and hyperinflation in their remaining native lung would cause ventilation–perfusion imbalance unfavorable to the transplant and might mechanically compromise the transplant in the event of mediastinal shift away from the native lung [45]. The technique of double-lung transplantation was, therefore, developed by the Toronto Lung Transplant Group and first used in humans in 1986 [5, 17, 37, 38]. However, this procedure is technically difficult, is associated with a higher incidence of ischemia and complications of the tracheal anastomosis, requires cardiopulmonary bypass and heparin therapy, and results in more morbidity than unilateral transplantation [4, 37]. In 1989, single lung transplantation was performed successfully in several patients with end-stage COPD [29, 52]. The surgery is technically simpler, and because it is more economical of available donor organs, should be considered the procedure of choice in suitable patients with nonseptic end-stage COPD.

Single lung transplantation has also been done in patients with primary pulmonary hypertension and Eisenmenger's syndrome due to congenital heart disease [26, 51]. Although it was initially thought that poor right ventricular function in these patients mandated transplantation of the heart in addition to the lungs, experience has shown this is not necessarily the case. The right ventricle, once relieved of chronic pressure overload, may recover function [6, 17, 51]. Acceptable levels of right ventricular function are difficult to define, but at our institution single lung transplantation for pulmonary hypertension is considered if the right ventricular ejection fraction is above 20% and if echocardiography shows that the ventricle is not severely diseased. There is less experience with single lung transplantation in this setting than with heart–lung transplantation, which has been the accepted approach, but the satisfactory results achieved with the simpler operation warrant its continued consideration.

Single lung transplantation is probably now the procedure of choice in appropriate patients with nonseptic end-stage lung disease. While pulmonary fibrosis, obstructive pulmonary disease, and pulmonary hypertension have comprised the majority of these patients, chronic respiratory failure from a variety of causes has been treated with transplantation. The numbers of these patients are small, but the list continues to expand as experience grows and the procedure becomes more widely available.

Single lung transplantation, however, is not a realistic option in patients with chronic septic lung disease, such as cystic fibrosis or bronchiectasis, because infection in the remaining native lung would compromise the transplanted lung, particularly in the setting of posttransplantation immunosuppression. The en bloc double lung transplantation referred to above has been successful in some patients requiring bilateral transplantation. However, because of the complicating factors of the procedure, the 2 lungs are now usually replaced by sequential replacement of each lung, with separate bronchial anastomoses rather than a single one at the trachea. In most cases, cardiopulmonary bypass is not required during the sequential procedure, unless the patient cannot be supported by the native lung during the first transplantation [4].

Table 2. Selection criteria for recipients

Age < 60 years
Limited life expectancy (<12–24 months)
Progressive deterioration in clinical status or progression of disease
Adequate right heart function
Not receiving corticosteroid therapy (patients receiving low dosages of prednisone may be considered)
Medically compliant
Stable nutritional status
Ambulatory
No coronary artery disease
No contraindications to immunosuppression
Adequate renal and hepatic function
No complicating systemic disease
Stable emotional support system

Table 3. Contraindications to single lung transplantation

Age > 60 years
Active systemic infection, human immunodeficiency virus disease, or hepatitis
Inadequate renal or hepatic function
Severe malnutrition
Prolonged endotracheal intubation
Prolonged, continuing high-dosage corticosteroid use
Cerebral vascular disease
Obesity
Recurrent active peptic ulcer disease or diverticulitis
Extrapulmonary systemic disease
Coronary artery disease or poor left ventricular function
Emotional or social instability
Tobacco, alcohol, or drug abuse
Severe chest wall deformities
Cancer
Medical noncompliance

Patient Selection

Again because donor organs are scarce, transplant recipients must be selected carefully. The criteria for transplantation as well as contraindications to transplantation are shown in Tables 2 and 3.

Age

The upper age limit for lung transplantation has been arbitrarily set at 60 years. The older patient must also be evaluated for potential presence of extrapulmonary disease.

Life Expectancy

Candidates for lung transplantation should have a limited life expectancy. The predictive indices differ for end-stage disease in the 5 most common diseases treated by lung transplantation: COPD, pulmonary fibrosis, primary pulmonary hypertension, cystic fibrosis, and Eisenmenger's syndrome. In patients with COPD from α_1-antitrypsin deficiency or any other cause, a severely decreased forced expiratory volume in 1 sec (FEV_1) generally correlates with worse survival rates [30]. The presence of hypoxia, hypercapnia, and cor pulmonale generally parallel the decline in FEV_1. End-stage cystic fibrosis is generally accompanied by severe obstruction as well as by a clinical decline due to bronchiectasis and recurrent pulmonary infection. End-stage pulmonary fibrosis is generally indicated by significant restrictive ventilatory defect on pulmonary function testing. Resting hypoxemia with oxygen desaturation on limited exercise and severe functional impairment are seen. Patients with end-stage primary pulmonary hypertension or Eisenmenger's syndrome usually show signs of significant pulmonary hypertension with high pulmonary artery and right atrial pressures, a decreased cardiac index, and oxygen desaturation with exercise. These patients generally are in NYHA functional class III or IV [26]. As mentioned above, right ventricular dysfunction was initially thought to indicate a need to replace both heart and lungs, but recent experience has shown that the right heart failure can be at least partially reversible after single lung transplantation [17, 26, 51]. Whether single lung or heart–lung transplantation is done in these patients depends on right ventricular performance.

Corticosteroids

Dehiscence of the bronchial anastomosis has been clearly shown to be related to preoperative corticosteroid therapy and, therefore, such therapy should be stopped before transplantation, preferably several weeks before [4, 13, 28]. Some patients wait for a donor organ for months, and maintaining the patient without steroid therapy can be difficult. In such cases, inhaled steroids or cytotoxic therapy may help to maintain the patient without compromising the transplantation. Patients receiving minimal doses of oral corticosteroids may be candidates for transplantation.

Psychosocial Issues

The actual process of transplantation is long and arduous, beginning with the initial referral and extensive evaluation at the transplant center. If the patient is deemed a candidate, an emotionally difficult period of waiting usually follows during which the patient needs to maintain nutritional status and physical well-being while discontinuing corticosteroid therapy. After transplantation, the patient remains under careful long-term medical observation for rejection or infection. The process is emotionally wearing. Therefore, the candidate recipi-

Table 4. Immunosuppressive therapy for lung transplantation

Preoperative
  Cyclosporin, 4–8 mg/kg orally; Adjust to baseline serum creatinine level
  Azathioprine, 4 mg/kg intravenously
  Methylprednisolone, 500 mg intravenously
Postoperative
  Horse antilymphocyte globulin, 10 mg/kg/day intravenously for 3–5 days
  Cyclosporin A, 7.5 mg/kg/day in divided doses every 12 hr
    Begin day 1–7 postoperatively depending on preoperative serum creatinine level
    Adjust dosages (3–8 mg/kg/day) to achieve serum cyclosporin level of 300–400 ng/ml in year
      1, 200–300 ng/ml in year 2, and 100–200 ng/ml in year 3 and later
    Azathioprine, 0.5–1 mg/kg/day; Adjust to maintain leukocyte count > 4500/mm^3
    Methylprednisolone, 125 mg intravenously every 8 hr × 3 doses
    Prednisone, begin 7–14 days postoperatively at 20 mg/day orally

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ent is also assessed by psychologists and social workers to ensure that he or she will be medically compliant and motivated and that emotional support is available. The presence of underlying psychiatric illness or a history of substance abuse is also considered before a patient undergoes the transplant procedure. It is imperative that the patient be medically compliant after transplantation.

Other Systemic Disease

The candidate for transplantation should be ambulatory, reasonably independent, and motivated enough to have good rehabilitation potential. Any active, potentially debilitating extrapulmonary systemic disease makes lung transplantation unrealistic, although systemic diseases with symptoms confined to the lung may be treatable by transplantation (e.g., sarcoidosis, scleroderma, lymphangioleiomyomatosis, eosinophilic granuloma). However, if there is systemic disease with extrapulmonary end-organ damage, lung transplantation generally cannot be recommended. Dysfunction of the liver or kidneys poses particular problems because of the need for therapy with cyclosporin and other immunosuppressive drugs after transplantation. Cardiac function should be thoroughly evaluated, with assessment of both right and left ventricular function and cardiac catheterization to rule out significant coronary artery disease.

Immunosuppression for Lung Transplantation

The immunosuppression regimen for patients undergoing transplantation varies among centers and must be tailored to each patient. The protocol used at our institution is shown in Table 4. The mainstay of therapy are cyclosporin, azathioprine, and prednisone. Cyclosporin and azathioprine do not immediately

suppress immune function, and, therefore, the regimen is supplemented in the early postoperative period by antilymphocyte globulin and corticosteroids [12].

Long-Term Management

Technical problems with the transplantation surgery itself have been extensively evaluated, but there remain postoperative issues pertaining to the bronchial anastomosis, specifically dehiscence and stenosis. Dehiscence fortunately is now rare, but bronchial stenosis may occur as a late airway complication, and has been addressed by bronchial dilatation as well as by placement of stents [37, 41].

The major posttransplantation complications are rejection and infection. Differentiating the 2 can be difficult, but is crucial because they account for the major morbidity and mortality associated with lung transplantation.

Rejection

The differential diagnosis of the posttransplantation patient with an abnormal chest radiograph with or without fever, gas exchange abnormalities, or worsening pulmonary function includes organ rejection, infection, and volume shifts. Diagnosis of rejection of the transplanted lung can be difficult. The chest radiograph may show diffuse or patchy infiltrates, consolidation, nodular densities, or pleural effusions, or it may be, in as many as 75% of cases, normal [12, 32]. Spirometry is often abnormal in the first several months after transplantation due to postoperative changes, and, therefore, pulmonary function tests are not useful in the early weeks, when patients often have their first episode of rejection [12]. Gas exchange abnormalities are also nonspecific in rejection. Perfusion scanning may show changes in blood flow to the transplanted lung, but is not sensitive and may not be practical in the critically ill patient [50]. The results on physical examination and the common clinical symptoms of cough, shortness of breath, or fever are also nonspecific.

The diagnosis of rejection is made on the basis of histologic evidence of rejection and the patient's response to methylprednisolone. Infection must be absent. The presence of a perivascular monocytic infiltrate with or without submucosal inflammation, eosinophilic infiltration, or extension into the interstitium in the absence of identifiable infectious pathogens is consistent with rejection [19, 32, 44, 46]. The patient should have a fairly acute response to treatment with pulse methylprednisolone (at our institution, 1 g intravenously [IV]/day for 3 days), usually with alleviation of symptoms and improvement in chest radiographs occurring within 24 hr [4].

Histologic confirmation of rejection requires biopsy. In the transplanted lung, repetitive biopsy is not as feasible or as easy as in solid organs such as heart or kidney. Repetitive open lung or thoracoscopic biopsy is unrealistic. Transbronchial biopsy and bronchoalveolar lavage have been useful, but only

small tissue specimens can be obtained, making diagnosis difficult, and bronchoscopy may be difficult to perform safely in the significantly ill or unstable patient [18, 19, 42, 44, 54]. However, the diagnostic yield of bronchoscopy has been reportedly as high as 85% if more than 4 fluoroscopically guided biopsy specimens are taken [19, 44]. Bronchoalveolar lavage is useful in identifying infection. Although it is obviously not helpful with histology, future consideration should be given to its potential role in the differentiation of rejection from infection. Proliferative responses in lymphocytes from bronchoalveolar lavage fluid from patients with lung transplants have been studied at the University of Pittsburgh and are believed to correlate with histologically confirmed infection [39]. It has been proposed that such evaluation may be a safe and reliable means of surveillance monitoring of these patients, analogous to endomyocardial biopsy in patients with cardiac transplants [20, 39]. Other such less invasive means of identifying rejection are needed.

Chronic Rejection

Chronic rejection of the transplanted lung is manifested as obliterative bronchiolitis. Tissue specimens show inflammation of distal bronchioles with eventual scarring and obliteration of small airways [12, 23, 46]. Radiographic findings are nonspecific, and the process can mimic infection. Obliterative bronchiolitis can occur at any time after transplantation, with presenting symptoms as mild as a slight cough. Routine surveillance of patient by transbronchial biopsy is difficult, and therefore physical examination and pulmonary function must be carefully monitored. A decline in midflow rates or FEV_1 can signal rejection [44, 47]. Early diagnosis of chronic rejection in patients with lung transplants is crucial because prompt institution of augmented immunosuppressive therapy may reverse or at least attenuate the obliterative process [21, 31]. However, high-dosage corticosteroids, increased cyclosporin dosage, azathioprine, antilymphocyte globulin, OKT3 monoclonal antibody, total lymphoid irradiation, and antibiotics have not consistently reversed or stabilized the disorder and there is currently no adequate treatment for obliterative bronchiolitis once it is established [23]. The course is generally relentless and progressive, with retransplantation being the only long-term alternative. Chronic rejection is currently the most common indication for retransplantation, but both operative and post-operative mortality in second transplants has been high [24]. The shortage of donor organs demands that every effort to prevent this difficult problem be made.

Infection

The lung is a major, if not the primary, site of infection in any patient with a transplanted organ. The patient with a lung transplant is at particularly high risk because such infection can compromise the transplanted organ itself. The

differential diagnosis of fever, cough, radiographic abnormalities, and shortness of breath unfortunately includes every possible infection as well as rejection.

Bacterial Pneumonia

The incidence of bacterial pneumonia, both early after surgery and at any point thereafter, is high. Before surgery, the donor lung is inspected for signs of infection, and cultures are taken; infection makes the lung unsuitable for transplantation. In the experience of the University of Pittsburgh, the incidence of bacterial pneumonia in the first 2 weeks after transplant was 35%, and overall was 66% [7], and was considered a major contributing factor in 47% of all their fatalities. Monitoring of tracheal secretions, culturing of bronchial specimens from bronchoalveolar lavage, and the use of broad-spectrum antibiotics have helped to decrease the incidence and morbidity of bacterial pneumonia, but it remains a serious problem in the patient with a lung transplant.

Viral Infection

Cytomegalovirus (CMV) is the second most common cause of pneumonia after bacterial infection. Diagnosis of CMV pneumonia is essential, because rejection can mimic its clinical presentation. A rise in CMV titer or detection of viremia is suggestive, but the diagnosis of CMV pneumonia requires either positive evidence of virus-induced changes in cells from bronchoscopic specimens or histologic confirmation in lung tissue. The growth of virus in cultures from bronchoscopic specimens or virus-induced changes seen with the rapid shell vial assay are also useful.

The organ recipient who is seronegative for CMV is extremely susceptible to CMV infection, particularly if the donor organ or transferred blood products are seropositive. In the experience from Papworth Hospital, there was an unacceptably high rate of CMV pneumonia in seronegative recipients of organs from seropositive donors [19, 43]. Matching of seronegative recipients with seronegative donors has dramatically decreased the risk of primary CMV infection.

The potential relationship of CMV infection with chronic rejection has been noted at several centers. Although obliterative bronchiolitis can occur in the absence of prior infection, primary CMV infection appears to place recipients at higher risk for its development [23, 25, 47]. Because obliterative bronchiolitis confers a poor prognosis, transplant recipients should be monitored for CMV infection and treated promptly if it occurs. Gancyclovir is the generally accepted therapy for CMV pneumonia but hyperimmune globulin has also been advocated at some centers. Gancyclovir or acyclovir prophylaxis may also be effective.

Other viruses can cause less severe infectious syndromes in lung transplant recipients. Herpes simplex infection can lead to lymphoproliferative disease, a mononucleosis-like syndrome, or pneumonia [7, 12]. Varicella zoster, hepatitis, and respiratory syncytial viruses have all been reported to cause infection in

the patient with lung transplantation, although symptoms are often extrapulmonary [7].

Fungal Infection

Fungal infections are uncommon after lung transplantation. However, deep-seated infections are difficult to eradicate in the immunosuppressed transplant recipient. Differentiating colonization from infection can be difficult, and protected brush specimens or semiquantitative cultures may be helpful. *Candida* and *Aspergillus* are the 2 most commonly detected organisms [7]. Cryptococcal infection has been reported, but it is rare [12].

Protozoal Infection

Like other immunosuppressed patients, recipients of lung transplants are susceptible to infection with *Pneumocystis carinii*. Prophylaxis with trimethoprim–sulfamethoxasole or aerosolized pentamidine is used, and the incidence of infection appears to be low [7, 12].

Conclusion

Because of the brilliant and intense effort by pioneers in transplantation research and practice, lung transplantation is now possible in previously untreatable patients. Major effort now needs to be directed at the difficult long-term care of these patients to improve their quality of life and help them live longer. The shortage of suitable donor organs and the long waiting lists of potential recipients at our institution and others mandate that patients fortunate enough to obtain an organ continue to receive the highest quality of medical care.

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