Current Status and Future of Lung Transplantation

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Abstract

Lung transplantation has been performed successfully outside Japan since 1983 in patients with end-stage lung disease. More than 9,000 lung transplants have been reported in The Registry of the International Society for Heart and Lung Transplantation. In contrast, a transplant law became effective in Japan only recently, and four universities were designated as official lung transplant centers (Okayama, Osaka, Kyoto and Tohoku Universities). In October 1998, the first successful living-donor lobar lung transplantation was performed at Okayama University. Since then, seven lung transplants (four from living donors and three from cadaveric donors) have been successfully performed in Japan. Although lung transplantation offers acceptable prospects for 5-year survival, chronic rejection and donor shortage remain to be major problems. In an effort to address the donor shortage issue, living-donor lobar lung transplantations have been performed with satisfactory intermediate survival and functional results. (Internal Medicine 40: 87-95, 2001)

Key words: living-donor lobar lung transplantation, bronchiolitis obliterans, donor shortage

Introduction

Since the performance of the first successful lung transplantation in 1983 (1), lung transplantation has gained wide spread acceptance as a therapeutic option for patients with various end-stage lung diseases. More than 9,000 lung transplants have been reported in The Registry of the International Society for Heart and Lung Transplantation (2). In contrast, it has been just recently that a transplant law has become effective in Japan; to date only seven lung transplants have been performed. This article reviews the current status of lung transplantation in the world and in Japan.

History

The first human lung transplantation was performed by Hardy et al in 1963 (3). Following that first unsuccessful attempt, approximately 40 patients underwent lung transplantation in medical centers throughout the world during the ensuing 15 years, but none of the recipients survived long term. Many of these patients were probably moribund at the time of transplantation. Aside from their pretransplant condition, the causes of death included respiratory insufficiency, pneumonia, rejection and airway complications (4).

The early results were disappointing but, with the advent of cyclosporine for improved immunosuppression (5), the first successful heart-lung transplantation was reported by the Stanford group in 1982 (6). Finally, truly long-term survival after single lung transplantation was achieved by Cooper and colleagues in Toronto, the first such operation being performed on November 7, 1983 (1). Three years later, the same group described the first successful series of en bloc double lung transplants (7). Although this procedure did have the definite attraction of preservation of the recipient heart, it was associated with a high incidence of airway complications (8). In 1989 the Washington University group described the technique of bilateral sequential single-lung transplant (9), a procedure that has required only minor modifications during the past decade.

Recipient Selection

A successful transplant program has many facets, and selection of suitable recipients is one of them (10). The recipient selection criteria varies somewhat among centers depending on the local experience and program emphasis. Recently, “International Guidelines for the Selection of Lung Transplant Candidates” was documented (11). In 1997, similar inclusion and exclusion criteria were established in Japan (Table 1). Following multidisciplinary assessment, a decision is made to accept or reject the patient as a potential lung transplant recipient by a local committee in official lung transplant centers. Candidates accepted by the committee are evaluated further by a nationwide Central Lung Transplant Evaluation Committee. Then, if accepted, they are listed by the Japan Organ Transplant Network.

In the USA and in Europe, the indications for lung transplantation continue to be dominated principally by chronic obstructive pulmonary disease, and cystic fibrosis is the most common indication for bilateral lung transplantation (2). In
Japan, young emphysema, α1-antitrypsin deficiency and cystic fibrosis are very rare. Different indications, such as primary pulmonary hypertension, bronchiectasis, lymphangioleiomyomatosis and idiopathic pulmonary fibrosis, were found in patients accepted for lung transplantation in our Center (12). It is important to keep in mind that these diseases have less favorable results after transplantation, generally (13).

Table 1. Inclusion and Exclusion Criteria for Lung Transplantation

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<th>General</th>
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<td>1. Progressive disease in spite of maximal medical treatment</td>
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<td>2. Limited life expectancy without lung transplant</td>
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<td>3. Age younger than 60 years for single lung transplant and 55 years for bilateral lung transplant</td>
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<td>4. Willingness to receive lung transplant with good family support</td>
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<td>5. Ability to receive postoperative routine examination and immunosuppressant</td>
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<th>Diagnoses</th>
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<td>1. Primary pulmonary hypertension</td>
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<td>2. Idiopathic pulmonary fibrosis</td>
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<td>3. Emphysema</td>
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<td>4. Bronchiectasis</td>
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<td>5. Pulmonary sarcoidosis</td>
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<td>6. Pulmonary lymphangioleiomyomatosis</td>
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<td>7. Secondary pulmonary hypertension</td>
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<td>8. Others</td>
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<th>Contraindications</th>
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<tr>
<td>1. Active infection in other than lung</td>
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<td>2. Other organ failure</td>
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<td>3. Poor nutritional status</td>
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<td>4. Active smoker</td>
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<td>5. Marked obesity</td>
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<td>6. Inability to participate in a rehabilitation program</td>
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<td>7. Psychosocial problem</td>
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<td>8. Alcohol or drug abuse</td>
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<td>9. No good family support</td>
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<td>10. Coagulopathy</td>
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<td>11. Extensive pulmonary adhesion</td>
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<td>12. Human immunodeficiency virus</td>
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Donor Selection and Lung Preservation

The lung is the most fragile organ in a patient who is brain-dead and it is subject to damage by excessive administration of fluid, aspiration, and ventilator-associated pneumonia. For this reason, less than 20 percent of cadaveric donors have lungs suitable for harvest. In 1997, donor inclusion and exclusion criteria were established in Japan (Table 2).

In certain circumstances, the donor selection criteria can be somewhat relaxed. A minor degree of pulmonary infiltrate can be accepted in a donor used for a bilateral transplant. Sundaresan et al reported that donors with marginal quality as judged by arterial blood gas analysis and radiographic assessment provided postoperative function equivalent to those judged excellent (14).

Because better lung preservation methods would increase the available donor numbers, facilitate logistics, and optimize the early function of the transplanted lung, numerous studies of lung preservation have been published and reviewed (15). In experimental studies, many investigators have suggested that extracellular preservation solution provides better pulmonary function than intracellular preservation solution (16–19). However, a high potassium solution such as Euro-Collins solution and University of Wisconsin solution have been used widely, with a safe preservation time of approximately 6 hours. In 1999, a German group reported that graft preservation using a low potassium solution lead to better immediate and intermediate graft function than Euro-Collins solution based on 80 clinical lung transplantations (20). In Europe and Canada, low potassium solution has become a standard preservation for lungs. Other preservation techniques such as retrograde perfusion via pulmonary veins (21) and controlled reperfusion with white cell-filtered blood (22) have been reported with encouraging results.

Choice of Surgical Technique

Heart-lung transplantation was the first procedure to be successfully performed (6), but it has largely been supplanted by procedures to replace the lung alone. It has been demonstrated that right ventricular function improves immediately after single or bilateral lung transplantation and with long-term follow-up, that improvement is maintained (23). Heart-lung transplantation is now used in patients with Eisenmenger's syndrome, and irreparable cardiac defects and in patients with advanced lung disease and concurrent left ventricular dysfunction or extensive coronary artery disease.

Patients with restrictive lung disease such as idiopathic pulmonary fibrosis (IPF) have been considered to be ideal candidates for single lung transplantation (SLT) (24). The native, remaining lung has markedly diminished compliance and increased vascular resistance, so that both ventilation and blood flow are preferentially directed to the transplanted lung. Meyers et al compared SLT and bilateral lung transplantation (BLT) for IPF and found no benefit of BLT over SLT with this diag-
nosis (25).

Obstructive lung disease, notably emphysema and α1-antitrypsin deficiency, have become the most common indication for lung transplantation (2). SLT (26) and BLT (27) have been used with success. BLT offers significant functional advantage in the long term (28). In SLT, progressive hyperinflation can occur, compressing the allograft and contributing to late deterioration in allograft function (29). In this setting, surgery to reduce the volume of the native lung has been reported to improve lung function (30). Lung volume reduction surgery (LVRS) achieves satisfactory improvement of disabling symptoms early after operation while avoiding immunosuppression and transplant-specific complications (31–33). LVRS as a bridge to lung transplantation has been successfully performed (34).

For infectious lung diseases, such as cystic fibrosis and bronchiectasis, BLT has been exclusively used. Although these patients usually grow *Pseudomonas aeruginosa* in their respiratory tract preoperatively, the risk of postoperative infection in these patients is no greater than that in other patient populations (35).

For patients with pulmonary hypertension, SLT and BLT have been successfully performed (36, 37). When SLT is performed, high vascular resistance in the native lung requires the allograft to handle nearly the entire cardiac output, potentially causing exaggerated pulmonary edema due to reperfusion and poor allograft function during the immediate postoperative period. However, a recent study of patients with pulmonary hypertension at the University of Pittsburgh found no difference in perioperative oxygenation, the duration of mechanical ventilatory support, or actuarial survival between SLT and BLT (38). Significant advances in long-term vasodilator therapy (39) have recently shown encouraging results in patients with primary pulmonary hypertension (PPH). Potential candidates for lung transplant with a diagnosis of PPH should be evaluated by a center with experience in vasodilator therapy.

**Postoperative Care and Immunosuppression**

Most patients are extubated within 24 to 48 hours of transplantation after standard ventilatory support. However, early severe graft dysfunction, as manifested by hypoxia and pulmonary hypertension, occurs in 10% to 20% of lung transplant recipients. A number of strategies have been developed in an attempt to reduce early allograft dysfunction, for example, use of oxygen-derived radical scavengers (40), pentoxifylline (41), and prostaglandin E1 (42). Inhaled nitric oxide improves oxygenation and decreases pulmonary arterial pressure without systemic circulatory effects and has been widely used (43).

Most clinical lung transplantation programs rely on triple-agent immunosuppression regimens consisting of cyclosporine, azathioprine, and corticosteroids. Some centers also use antilymphocyte-antibody preparations during the induction phase, but there is no convincing evidence that this approach diminishes the incidence of acute or chronic rejection (44). A Pittsburgh group has conducted a randomized prospective trial to compare tacrolimus and cyclosporine after lung transplantation (45). They found a potential advantage of tacrolimus in reducing the risk of chronic rejection. Encouraging results of mycophenolate mofetil (MMF) as alternative to azathioprine have been reported (46, 47). The combination of tacrolimus and MMF has become standard immunosuppression therapy in some centers.

The rate of infection among lung transplant recipients is several times higher than that among recipients of other organs and is most likely related to the exposure of the allograft to the external environment. All patients are given routine antibacterial prophylaxis. If indicated by cultures of bronchial secretions from the donor or recipients, adjustments in these antibiotics are made. Cytomegalovirus remains a significant problem. Most programs have adopted the strategy of matching seronegative donors to seronegative recipients. Other recipients should receive prophylaxis with intravenous or oral ganciclovir (48).

The use of radiographic, clinical and physiologic criteria has been insufficient to delineate infection from rejection. Transbronchial lung biopsy offers a safe and accurate means of diagnosis of acute rejection and has emerged as the procedure of choice (49).

**Airway Complications**

In the early days of clinical lung transplantation, dehiscence of the bronchial anastomosis was a frequent source of mortality (4). Based on a series of laboratory investigations by Cooper and colleagues, routine use of omentopexy (50) and avoidance of high-dose perioperative corticosteroids (51) were thought to be key strategies for the first successful human lung transplantation in 1983. However, recent studies have demonstrated that omentopexy is not essential (52) and early postoperative corticosteroids do not impair airway healing (53). Donor and recipient peribronchial tissue is used to cover the anastomoses. There seems to be no difference in the airway complication rate between telescoped (54) and end-to-end anastomosis (55). Direct bronchial revascularization has been reported with low rates of airway complication, however this technique has been used in few centers. Experienced centers have recently reported the incidence to be less than 5% (56).

**Bronchiolitis Obliterans Syndrome**

Posttransplantation bronchiolitis obliterans syndrome (BOS) is a clinicopathologic syndrome characterized physiologically by airflow limitation and histologically by bronchiolitis obliterans (57). BOS is considered a manifestation of chronic allograft rejection, and it is the most problematic late complication of lung transplantation. The pathogenesis of bronchiolitis obliterans remains poorly understood. However, the identification of acute rejection as the single most important risk factor substantiates the hypothesis that this disorder is immunologically based (58, 59). Other proposed risk factors include cytomegalovirus infection (60), airway ischemia (58), and HLA mismatching (61).
Various treatments have been used for BOS, including anti-lymphocyte antibodies (62), tacrolimus (63), inhaled cyclosporine (64), and simultaneous bone marrow transplantation to induce chimerism (65), but no single approach has proved superior. In the absence of effective treatment for BOS, attention has focused on preventive strategies. Many centers perform frequent biopsies for surveillance in the hope that early detection and treatment of clinically occult acute rejection will decrease the risk of chronic rejection.

Outcomes

Although lung transplantation had shown continued growth through 1993, this growth has clearly ceased despite the use of increasingly marginal donors (Fig. 1). Consequently, an increasing number of candidates die while awaiting transplantation. The actuarial survival for SLT and BLT is shown in Fig. 2. The survival curves appear to be diverging after 3 years post transplanta-
plantation with BLT having a survival advantage (p<0.005). The 5-year survival was 49% for BLT and 40% for SLT. Survival rates for lung transplantation have improved only moderately over the past 10 years despite refinements in surgical technique and postoperative care. These rates lag considerably behind those for heart and liver transplantation, for which 5-year actuarial survival approximates 70%. Experienced centers tend to have better outcomes, hospital death less than 10% and 5-year survival approaching 60% (66).

Among operative survivors, functional results are excellent. The usual patient is returned to normal levels of exercise tolerance without oxygen supplementation within 6 to 8 weeks of transplantation. For patients with obstructive, restrictive or infectious lung diseases, lung transplantation offers significant improvement in pulmonary function and gas exchange (67). When performed in patients with pulmonary hypertension, both SLT and BLT result in immediate and sustained normalization of pulmonary vascular resistance and pulmonary arterial pressures. This is accompanied by an immediate increase in cardiac output.

**Living-donor Lobar Lung Transplantation**

Transplantation of lobes from two healthy living donors is a recently developed technique by Starnes’s group (68). The procedure, living-donor lobar lung transplantation (LDLLT), involves bilateral implantation of the lower lobes from two blood group-compatible living donors (Fig. 3). The procedure has been performed almost exclusively in patients with cystic fibrosis, though the indications have recently been broadened (69). Because a limited amount of lung tissue is transplanted, this type of operation is performed under cardiopulmonary bypass and seems to be best suited for children and small adults. The donors should be larger than the recipient so that the donor lobes fill each hemithorax, thus avoiding persistent pleural-space problems in the recipient. However, the amount of tolerable size discrepancy between donors and recipients is currently unknown.

LDLLT offers an alternative for patients with a life expectancy of less than a few months. Although patients are much sicker in LDLLT, intermediate-term functional and survival outcomes approximate those achieved with conventional transplantation of cadaveric lungs (70). Donor outcomes are as important as recipient outcomes in this procedure. A clinical series involving 120 donors reported no deaths and only four serious complications necessitating surgical re-exploration (71). Donation of a lobe decreased lung volumes by an average of approximately 15% and was not associated with a long-term limitation in activity.

Starnes and colleagues recently reported that pediatric patients receiving LDLLT had less BOS and better pulmonary function than those receiving conventional transplantation of cadaveric lungs (72). They concluded that LDLLT should be the preferred method of lung transplantation in children whenever possible.

**First Successful Living-Donor Lobar Lung Transplantation in Japan**

Our group, from Okayama University, performed the first successful LDLLT on October 28, 1998 (73). A summary of this case follows;

In September 1998, a 24-year-old woman with primary ciliary dyskinesia began suffering severe respiratory insufficiency and right-sided heart failure after multiple respiratory infections. Chest X-ray showed normal cardiac situs and diffuse bilateral opacification due to generalized bronchiectasis (Fig. 4). The woman had bacterial tracheobronchial tract colonization by *Pseudomonas aeruginosa* and *Staphylococcus epidermidis*, managed with antibiotics. On October 13, she required mechanical ventilation and a tracheostomy. Right-sided heart failure was observed with a pulmonary artery pressure of 65/35 (47) mmHg. Despite maximal mechanical ventilation, arterial carbon dioxide tension reached 150 mmHg on October 28, at which time she underwent bilateral living-donor lobar transplantation with her sister’s right lower lobe and her mother’s left lower lobe under cardiopulmonary bypass. Transmission electron microscopy (TEM) of the removed bronchus showed in cilia cross-section that an inner dynein arm deficiency existed. Except for a short lung edema episode requiring nitric oxide inhalation on postoperative day 2, the subsequent course was relatively uneventful. Postoperative immunosuppression involved triple drug therapy of cyclosporine, azathioprine, and prednisone. Two episodes of acute rejection required intravenous high-dose methylprednisolone. Serial bronchoscopic examinations showed satisfactory healing in bilateral bronchial anastomoses. Pulmonary artery pressure became 30/13 (20) mmHg at 2 months. The patient was discharged 61 days after transplantation symptom-free and without the need for supplementary oxygen.

The patient was readmitted with a diagnosis of bacterial...
pneumonia (*Pseudomonas aeruginosa*) in the left lung at 4 months postoperatively; this was successfully managed by antibiotics. Other than this short-term readmission, she has been in good physical condition and returned to a normal, unrestricted lifestyle. The two donors have also recovered fully and returned to their previous lifestyles. One year after transplantation, her chest X-ray demonstrated well-expanded grafts with no detectable dead space (Fig. 5).

Serial changes in the recipient’s pulmonary function up to 18 months are depicted in Fig. 6. Her forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV₁) increased gradually, and these improvements were not associated with emphysematous change in transplanted grafts, since FEV₁% was stable after 6 months. These were further confirmed by stable functional residual capacity (FRC), residual volume (RV), total lung capacity (TLC), and RV/TLC after 6
Lung Transplantation

months. Serial arterial blood gas analysis showed satisfactory gas exchange. Gradually improving exercise capacity was confirmed objectively by the increase of a 6-minute walking distance.

Changes in FVC of the donors and recipient at 1 year are summarized in Table 3. Preoperatively, her sister’s FVC was 3,400 ml and her mother’s 3,020 ml. Given that the right lower lobe consists of 5 segments and the left lower lobe of 4, total FVC of the 2 grafts was estimated to be 1,530 ml (3,400 ml×5/19+3,020 ml×4/19), or 51.7% of the recipient’s predicted FVC (2,960 ml). One year after transplantation, the decline in FVC was 410 ml (12.1%) for her sister and 440 ml (14.6%) for her mother, making the total FVC decline in the donors 850 ml. The recipient’s FVC at 1 year became 2,160 ml, or 73.2% of her predicted FVC.

Current Status of Lung Transplantation in Japan

The history of lung transplantation in Japan has had a long dark period because of the difficulty in accepting the concept of brain death. The transplant law finally became effective in October 1997, and four official lung transplant centers (at Okayama, Osaka, Kyoto and Tohoku Universities) were designated in April 1998.

Receiving lung transplantation in other counties is an option for Japanese patients (74). A total 6 Japanese patients (including 2 patients from our center) have undergone lung transplantation in the USA. They are all alive and doing well, during a follow-up period to date of 27 to 80 months. This is a very encouraging result. However, this option contains a lot of obstacles including high cost (over $400,000), a long waiting time, language difficulties, the support system, and the ethical issue. It should be noted that donor shortage is also severe in USA.

During the past 7 years, 22 patients were accepted as candidates for lung transplantation in our center (12). Two of those with primary pulmonary hypertension went to the USA and there received bilateral lung transplant. Two patients received living-donor lobar lung transplantation in our center. These four recipients are alive and doing well during the follow-up period of 3 to 80 months. In contrast, among the 18 patients who have not received lung transplant, 8 patients have died while waiting. The survival of the candidates is quite limited without receiving lung transplantation.

Eight brain death donors have become available since February 1999 and two donors were suitable for lung transplantation. The first lung transplantation from cadaveric lung was performed on March 29, 2000. The donor lung was found in Tokyo and there split in two. The right lung was implanted in a patient with lymphangioleiomyoymatosisis at Tohoku University and the left lung was implanted in a patient with idiopathic pulmonary fibrosis at Osaka University. In spite of the relatively long ischemic time, approximately 5 hours, both procedures went well. Both patients were discharged 3–4 months after transplantation without need for supplementary oxygen.

Seven lung transplants have been performed in Japan so far (Table 4). Six of which were performed within the last 7 months. Four were LDLT. All seven patients are currently alive. Japanese transplant centers should be congratulated for achieving excellent results in their starting phase.

Because living-donor lobar lung transplantation requires two healthy donors with a compatible blood type and larger lung than the recipient’s, such a method is not available for most candidates. Therefore, this operation would not be a sufficient solution for the donor shortage. Since the survival of the candidates is quite limited without receiving lung transplantation, living-donor lobar lung transplantation is a realistic option for properly selected candidates. The current transplant law in Japan, the strictest one in the world, may need to be adjusted in the near future to expand the donor pool.

References


