PATIENT CARE

Lung Transplantation

Several Southeast Asian centers are now able to offer this treatment for carefully selected patients.

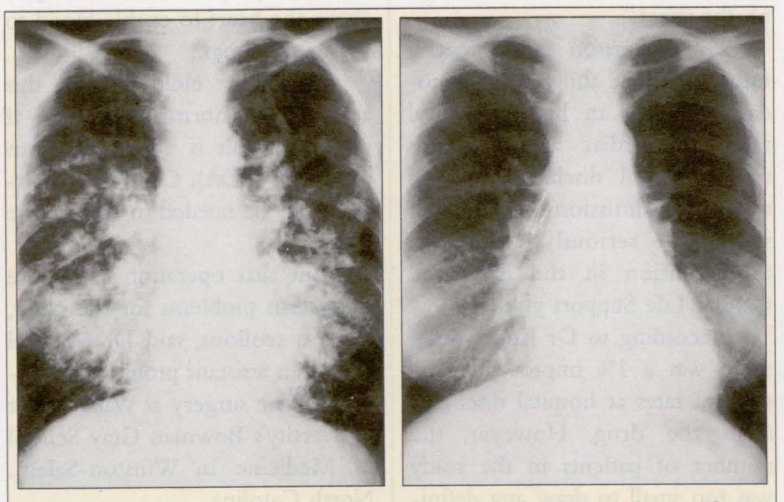
Professor Mary Ip *and* Drs Joseph Lee *and* Cheung Man-tat *describe the surgery and its indications and outcomes.*

Since the first successful heart-lung transplantation in 1981, lung transplantation in its various forms — heart-lung, single lung, double lung, and perhaps also lobar transplantation — has become a real possibility for a wide range of end-stage cardiopulmonary diseases for selected patients.

By February 1996, the International Society of Heart and Lung Transplantation Registry had recorded 6993 heart-lung or lung transplantations performed worldwide in over 120 transplant centers. This includes 1954 heart-lung (HLT), 1845 double/bilateral lung (DLT), and 3194 single lung (SLT) transplants. The number of DLTs has increased since 1990, while that of SLTs has plateaued.

Fewer heart-lung procedures are being performed, probably due to a shortage of heart-lung blocs, as well an increasing use of alternative procedures.

In Asia, the first HLT, SLT, and DLT operations were performed in 1988, 1991 and 1993 respectively. There is no reliable data on how many lung transplants have been performed in the region.



Chest X-rays showing bronchiectasis pre- and post bilateral transplant

Recipient selection

The indications and contraindications for lung transplantation are outlined in Table 1. In most centers, the upper age limit for HLT and DLT is 50 years, while SLT may be considered up to the age of 60 years. Patients should be considered for lung transplantation only if they have irreversible pulmonary vascular or parenchymal lung disease with progressive worsening respiratory failure despite optimal medical therapy. In practice, most patients awaiting transplant will have an FEV_1 less than 30% predicted and an estimated life expectancy of 18 to 24 months.

Patients must have a strong wish for transplantation and be psychologically stable.

Noncompliance with medical treatment, including failure to give up smoking is an absolute contraindication to transplant. Such patients are unlikely to cooperate with post-transplant follow-up or comply with rigorous immunosuppressive regimens.

Other contraindications include pre-existing malignancy, active mycobacterial or *Aspergillus* infection, and infection with hepatitis B or C virus and human immunodeficiency virus (HIV), all of which can progress when the patient is immunosuppressed.

Major renal or hepatic dysfunction is also a contraindication since tolerance of immunosuppressive agents will be poor. Poor nutritional status (body weight less than 80% predicted) and chronic steroid administration (over 10 mg to 15 mg prednisolone daily) are strong contraindications. They will slow wound healing, increase the risk of infection and delay post-operative recovery.

Previous thoracic surgery or pleurodesis increases the risk of perioperative bleeding, especially if cardiopulmonary bypass and anti-coagulation are needed. However, with the use of aprotinin and laser coagulation, bleeding can be minimized and transplantation can still be considered.

Patients with diabetic mellitus may pose an additional risk but can be accepted for transplantation provided there is no microvascular or end organ involvement. Some patients with collagen vascular disease may also be transplanted but those with systemic lupus erythematosus have a high incidence of thromboembolic complications and are therefore unsuitable candidates.

Although successful transplants have been performed in ventilated patients, the results are generally poor and most transplant centers consider these patients unacceptable candidates. Nevertheless, non-invasive positive pressure ventilation may be used as a bridge to transplantation.

Table 1. Lung transplant indications and contraindications

Indications
Severe chronic respiratory failure despite optimal medical therapy
Severely impaired quality of life
Patient positively wants a transplant
Age less than 60 years (50 years for HLT)
Absolute contraindications
Active mycobacterial or *Aspergillus* infection
Infection with HIV, viral hepatitis B or C
Noncompliance with treatment/medical advice
Other end-organ failure
Prednisolone therapy >15 mg daily*
Gross malnutrition
Risk factors
Previous thoracic surgery/pleurodesis
Preoperative ventilation
Collagen vascular disease, especially SLE

** Some only accept <10 mg daily. Most will exclude candidates with cushingoid features.*

Pretransplant assessment

After history taking and physical examination, a range of blood tests are required; in particular, the serological status of HIV and hepatitis B and C. Infective screening also includes serology to cytomegalovirus (CMV), Epstein Barr virus, herpes simplex virus and *Toxoplasma* and sputum for bacterial, fungal and mycobacterial cultures. Cardiopulmonary function assessment includes a lung function test, blood gas analysis, exercise capacity (a six-minute walk or stair climbing), electrocardiogram and two-dimensional echocardiogram, and in some cases cardiac catheterization.

A computerized tomogram of the thorax is often performed to assess the severity of initial parenchymal disease and the degree of pleural thickening/adhesion which may make surgery difficult. A lung perfusion and/or ventilation scan is indicated in SLT to determine the side for transplantation. In general, if a significant discrepancy exists between the two lungs, the less perfused side should be selected for transplantation.

Assessment of psychological suitability and quality of life is undertaken and patients are introduced to the transplant team. Dental, ear, nose and throat examination will be arranged when indicated as these may become sources of infection post-transplant.

It is difficult for the doctor to decide when to add a patient's name to the waiting list for transplantation and, if there are patients with similar lung volumes and same blood group, their relative priority on the list.

In addition to blood group and lung volume, dynamic components such as the current rate of decline of lung function or performance status, frequency and severity of pulmonary sepsis, operating time in each patient, and the average waiting time for donor organs must be considered.

This is especially important for disease conditions such as bronchiectasis, where a reliable estimation of survival may not be possible. It must be emphasized again that only patients who have had maximum medical treatment should be considered for transplantation, as the current mortality following lung transplantation remains substantial (around 30%).

On the other hand, delays in listing may result in patients being too ill for transplantation or dying while awaiting transplantation.

Choice of procedure

The current indications for various lung transplant procedures are summarized in Table 2.

For a recipient with a relatively normal heart, transplantation of the heart-lung bloc is wasteful. The transplanted donor heart may predispose the recipient to additional problems such as acute cardiac rejection or accelerated coronary atherosclerosis. In some centers, the recipient's heart, if healthy, is used for cardiac transplantation in another patient (the so-called "domino" procedure). As more and more patients are successfully transplanted with DLT and SLT, the only primary indication for HLT will be Eisenmenger's syndrome with a surgically incorrectable cardiac defect or pulmonary hypertension with severe irreversible cardiac dysfunction.

SLT is technically simpler and is performed via a conventional lateral thoracotomy and cardiopulmonary bypass is usually not required. It is suitable for most nonseptic parenchymal lung diseases and primary pulmonary hypertension (PHT). It economizes the use of donor organs since a pair of donor lungs can be shared between two recipients (a "twinning" operation).

In PHT patients, SLT is associated with a slightly higher mortality and morbidity — especially during the early post-transplant period — compared with DLT. This may be due to severe reperfusion injury in the donor lung resulting in a higher incidence of primary graft failure when the native lung, having extremely high pulmonary vascular resistance, is unable to provide the necessary buffering during the early implantation period.

Despite this, many PHT patients are still transplanted with SLT, especially in some US centers, due to a severe shortage of donor organs.

Bilateral sequential lung transplantation (BSLT) is the procedure of choice for DLT. It is indicated in septic lung conditions such as bronchiectasis or cystic fibrosis. It can also performed in instances where SLT would be an option and provides a better respiratory reserve for the recipients, especially because post-transplant bronchiolitis obliterans leading to impairment of graft function is so common. Thus, there is a tendency to offer BSLT for nonseptic indications, especially in younger recipients, but this must be balanced against the shortage of donor organs.

Donor selection

The lung is a very delicate organ and tolerates warm ischemia poorly. Hence, only heart-beating brainstem-dead donors are suitable, although animal research is underway to explore the possibility of cadaveric lung transplantation.

To guarantee that the donor lungs are healthy and free from infection, certain criteria based on clinical, radiographic, and gaseous exchange parameters are applied when screening suitable donors.

The ideal lung-heart bloc is obtained from a young non-smoker with no history of pulmonary, cardiac or malignant disease, no evidence of chest trauma or infection, a clear chest X-ray and normal gaseous exchange. The donor should not have received mechanical ventilation for less than 72 hours.

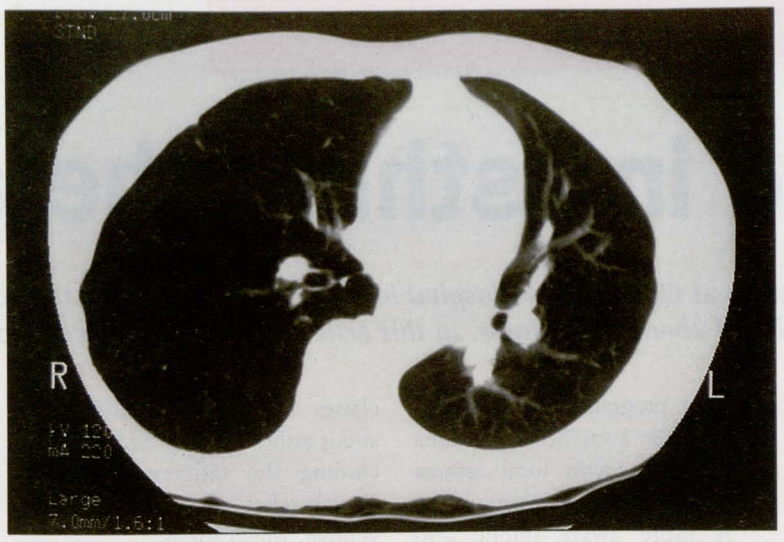
Although the absolute cut-off point on individual parameters may vary slightly among centers, the general principles are similar. A center's willingness to accept "borderline" donor lungs depends on the its degree of desperation.

Donor-recipient matching is based on ABO blood group compatibility, size of thoracic cage and CMV antibody status. Size matching is essential in lung transplantation as an oversized organ results in uneven ventilation due to compression (atelectasis) and, more dangerously, organ edema and intrathoracic tamponade with severe hemodynamic consequences.

On the other hand, an undersized organ results in hyperinflation, prolonged airleak, pleural effusion or empyema formation. Sepsis associated with prolonged intercostal drainage can be fatal in the immunosuppressed patient.

Size matching estimates are made using chest X-ray, submammary perimeters and "predicted" total lung capacity based on height, sex and age.

Matching of CMV status is beneficial as primary CMV pneumonitis resulting from seromismatched transplantation (seropositive donor to negative recipient) results in an extremely high mortality rate (up to 22%) despite treatment. Although many centers adopt a strict CMV-matching policy, CMV-mismatched transplantation may not be completely avoidable in centers with severe donor shortage. Some centers may rely on post-transplant CMV prophylaxis to ensure recipients remain CMV negative.



A diseased lung with single lung transplant

In Western countries, approximately 60% of the adult population is CMV antibody positive and the figure is likely to be even higher among Asian countries (> 80%).

HLA typing and matching is currently not feasible due to the short organ ischemic time (roughly six to eight hours) allowed and severe shortage of donor organs. However, preliminary retrospective data suggest better graft survivals and lower incidence of obliterative bronchiolitis are associated with fewer HLA mismatches. On the other hand, humoral sensitization is relatively uncommon in lung transplantation, and routine checking of panel-reactive antibodies is unnecessary and does not seem to affect outcome.

Complications

In the immediate post-transplantation period, hemorrhage and early graft dysfunction are the most common complications. Acute rejection and infection are the main problems during the first three months, and obliterative bronchiolitis and infection become major causes of morbidity and mortality thereafter.

Infection remains an important cause of morbidity and mortality in both early and late post-transplantation periods. Overall, the incidence of infection is extremely high in the first three months, accounting for as many as 50% of deaths in that period, decreasing to a relatively stable rate after one year. However, the infection rate increases again whenever augmentation of immunosuppression is required to treat rejection episodes.

Bacterial and fungal infections are dominant in the first postoperative month. CMV infection is most common in the second month, while *Pneumocystis carinii* pneumonia usually occurs between four and six months after transplantation.

In addition to infection, acute rejection is another major problem for all patients. Onset ranges from a few days to years after transplantation. The highest prevalence is again in the first three postoperative months.

The presentation of acute rejection is nonspecific, including symptoms such as fever, shortness of breath, chest tightness, decreased exercise tolerance, fatigue, lethargy, or a 10% to 15% reduction in home spirometry performance.

It is often difficult to differentiate on clinical or radiological grounds whether the patient is suffering from rejection or infection, and fibreoptic bronchoscopy and/or transbronchial biopsies are often required for a definitive diagnosis.

The standard treatment, which is effective in most cases, is intravenous pulse methylprednisolone for three days, followed by augmentation of maintenance steroid dosages. However, for recurrent and resistant acute rejection, immunosuppressants such as rabbit antithymocyte globulin (RATG) or OKT3 may be considered.

With advances in surgical techniques and immunosuppressive agents, early patient survival has markedly improved. The development of obliterative bronchiolitis (OB) in long-term survivors has now become the most important determinant of well-being and survival. Various series showed that 43% to 62% of long-term heart-lung survivors, and 25% to 31% of single or double lung transplant survivors, have developed OB.

The precise etiology of OB has not yet been defined, though it is now believed to be a form of chronic airway rejection secondary to recurrent or persistent severe acute rejection, CMV infection or HLA mismatching.

OB usually presents nonspecifically with dry unproductive cough, chest tightness, wheezing and increasing breathlessness. Serial lung function tests reveal a combination of severe obstructive and mild restrictive pattern, with minimal disturbance to the lung diffusing capacity.

OB is pathologically defined as submucosal scarring of the membranous and respiratory bronchioles, leading to eccentric, concentric or total obliteration of bronchiolar lumens. Because of its patchy and focal involvement, reports of diagnostic yields from transbronchial lung biopsy have varied widely, from 15% to 87%.

In 1993, an international working group established a clinical definition for the classification and grading of pulmonary graft dysfunction after transplantation, utilizing mainly lung function parameters. The term bronchiolitis obliterans syndrome (BOS) was adopted. It has been estimated that only 45% of lung transplant patients remained OB-free at the end of five years, and the overall median survival time from first diagnosis of BOS was reported to be about 30 months.

To date, there is still no definite treatment for OB. Since OB is believed to be a manifestation of chronic graft rejection secondary to recurrent severe acute rejection, current management should focus on early detection and treatment of rejection episodes, as well as on more effective maintenance immunosuppression, so as to decrease the incidence of OB.

Prognosis

With improvement in organ preservation techniques, immunosuppressive agents, diagnostic techniques and more effective treatment of CMV pneumonitis, one-year survival rates for HLT, SLT and DLT are 60%, 70% and 70%, and five-year survival rates are 37%, 39% and 47% respectively.

In selected centers, the one-year survival can be as high as 90% for SLT, 87% for DLT and 75% for HLT. There is approximately 15% improvement in survival rates from transplants performed from 1992-94 compared with those performed in the early era (1983-89).

Conclusion

Lung transplantation is an invaluable treatment modality for many patients suffering from end-stage lung disease. However, due to the marked shortage of organ supply worldwide, at least 20% to 25% of patients who are on the waiting list for transplantation die from their disease while waiting for donor organs.

Most Southeast Asian countries are still at the starting point in the development of lung transplantation. Results will only improve as experience increases with more transplants performed.

Since the shortage of donor organs is a great problem in Asian societies, it is important and urgent for the medical profession to publicize the issue. It must enhance awareness of the need for organ donation and educate the public on its benefits for patients as well as for the advancement of medicine. ■

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Table 2. Indications for different transplant procedures

Heart-lung transplantation
1. Eisenmenger's syndrome
2. Primary pulmonary hypertension*
3. Bronchiectasis/cystic fibrosis with cor pulmonale*
4. Miscellaneous: combined end-stage heart and lung disease

Single lung transplantation
1. Emphysema/chronic obstructive airways disease*
2. Cryptogenic fibrosing alveolitis*
3. Primary pulmonary hypertension*
4. Sarcoidosis+
5. Miscellaneous: 1-antitrypsin deficiency, lymphangio-leiomyomatosis+ etc.

Double lung transplantation
1. Bronchiectasis/cystic fibrosis*
2. Primary pulmonary hypertension*

** Most common indications for lung or heart-lung transplantations worldwide.*
+ Recurrence of disease in the allografts reported.

Case Study

Ms L is a 33-year-old woman with a history of bronchiectasis since age 11 and chronic productive cough throughout adolescence and adulthood. Both chest X-ray and computerized tomography of the thorax confirmed bilateral severe cystic bronchiectasis. Immunoglobulin levels and ciliary function were normal, and no specific primary etiology could be identified.

Her symptoms progressively deteriorated despite maximal medical therapy and she developed frequent severe bronchopulmonary sepsis. She became oxygen dependent, chairbound and required noninvasive positive pressure ventilation for respiratory failure that occurred during exacerbations. Lung function tests showed a mixed obstructive and restrictive pattern (FEV_1/FVC = 0.8/1.63).

In view of her progressively worsening respiratory function, with recurrent severe pulmonary sepsis and acute on chronic hypercapnic respiratory failure, she was referred for lung transplantation.

Since her cardiac function was well preserved, bilateral sequential lung transplantation was the preferred option and was performed.

She required multiple courses of antibiotics to control bacterial infections as well as prophylactic liposomal amphotericin B and itraconazole because her airways were colonized with *Aspergillus* and other fungi pre- and post- transplantation. She was discharged on day 38 post-transplant.

Forty-five days after transplantation she developed respiratory distress and collapse of the left lung. Bronchoscopy revealed bronchomalacia of the left main bronchus and moderate stenosis of both bronchial anastomoses.

Bilateral bronchial stenting using metallic stents was performed with rigid bronchoscopy under general anesthesia.

Her recovery was uneventful apart from an episode of pneumonia which was successfully treated with antibiotics.

Five months after transplantation she was well with no respiratory symptoms. Lung function showed marked improvement with FEV_1/FVC = 2.31l/2.45l.