Lung and heart-lung transplantation in Hong Kong

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Objective. To review the donor and recipient selection criteria, surgical techniques, perioperative and postoperative management, and complications of lung/heart-lung transplantation.
Data sources. *Medline* and non-*Medline* search of the relevant English literature, local data, and personal experience.
Study selection. Studies containing supporting evidence were selected.
Data extraction. Data were extracted and analysed independently by the authors.
Data synthesis. Lung/heart-lung transplantations are considered only for patients who have progressively disabling and end-stage disease. Numerous investigations of the recipient and rigorous matching between the donor and recipient are required. Factors such as maintaining the donor's haemodynamic stability, graft preservation, effective perioperative immunosuppression, and careful postoperative monitoring are key to a successful transplantation. Follow-up should include the home-monitoring of body weight, temperature, and spirometry, as well as regular chest X-rays, pulmonary function tests, and blood tests. So far, two double and two single lung transplantations, and one heart-lung transplantation have been performed in Hong Kong.
Conclusion. Lung transplantation is an invaluable treatment modality for patients with end-stage lung disease.

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Key words: Graft survival; Heart-lung transplantation; Intraoperative care; Lung transplantation; Patient selection; Postoperative complications; Treatment outcome

Introduction

Since the first successful heart-lung transplantation (HLT) in 1981,[1] HLTs and single and double lung transplantations (SLTs and DLTs) have been increasingly performed to treat a wide range of end-stage cardiopulmonary diseases. Improvements in organ preservation techniques, immunosuppressive treatment, and diagnostic procedures have led to average 1-year survival rates for HLT, SLT, and DLT of 60%, 70%, and 70%, respectively; the corresponding 5-year survival rates are 37%, 39%, and 47%, respectively.[2] However, owing to the paucity of donor organs and various technical problems, it was not until July 1995 when the first lung transplantation was successfully performed in Hong Kong.

This article reviews the indications and contra-indications, recipient assessment, donor and recipient selection criteria, organ procurement, surgical techniques, perioperative management, and common complications of lung transplantation.

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Indications and contra-indications for transplantation

Lung transplantations and HLTs are considered only for patients who have symptomatic, progressively disabling, and end-stage pulmonary and/or cardiac diseases, for which alternative medical treatment is not available and the estimated patient survival time is less than 18 months. Transplantation should not be offered to acutely ill patients, even in desperate situations. Indications for HLT and the various options of lung transplantation vary according to the aetiology of the lung disease and to the cardiac function.[3] Heart-lung transplantation is indicated by primary pulmonary hypertension, heart diseases that are complicated by pulmonary hypertension (eg Eisenmenger's syndrome), and lung diseases that are associated with cor pulmonale disease (eg cystic fibrosis). Single lung transplantation is suitable for patients with non-suppurative pulmonary disease (eg emphysema, cryptogenic fibrosing alveolitis, α1-antitrypsin deficiency, sarcoidosis) or other conditions such as lymphangioleiomyomatosis or bronchiolitis obliterans.

Double lung transplantation is required for suppurative pulmonary disease (eg bronchiectasis and cystic fibrosis) and primary pulmonary hypertension.

Although criteria vary among transplantation centres, HLT and DLT are usually performed for patients younger than 50 to 55 years, and SLT for those younger than 60 to 65 years. The presence of an underlying malignant tumour or infection with human immunodeficiency virus (HIV) is an absolute contra-indication, because of the expected reduction in survival time. Chronic renal failure and chronic liver disease (hepatitis B or C) are also contra-indications, because of the marked kidney and liver toxicities of the immunosuppressive drugs used in transplantation. Infection with *Burkholderia cepacia*, a bacterium which is resistant to multiple antimicrobial drugs, has been considered an absolute contra-indication by some transplantation centres due to the associated increase in morbidity and mortality after transplantation.[4] Refusal to abstain from smoking, drug abuse, serious psychiatric illness, and non-compliance to medical treatment are also absolute contra-indications for transplantation.

Having an autoimmune disease, such as systemic lupus erythematosus, is a relative contra-indication, as the disease reduces post-transplantation survival rates secondary to complications from underlying vasculitis.[5] Giving preoperative maintenance steroid therapy of a dosage greater than 0.3 $mg \cdot kg^{-1} \cdot d^{-1}$ of prednisolone (or an equivalent drug) frequently slows wound healing[6] and thus increases subsequent morbidity and mortality. A chronic dependency on mechanical ventilation results in difficult preoperative assessment and increased postoperative infective risks, while poor nutritional status (a patient weighing less than 80% of the appropriate ideal body weight) also undermines the likelihood of postoperative recovery. Intrathoracic conditions that are relative contra-indications to lung transplantation include sarcoidosis (which often relapses in the transplanted lung),[7] severe chest wall deformities, and previous pleurectomy, pleurodesis, or sternotomy; the technical difficulties associated with transplantation in patients with these conditions result in increased bleeding during the operation.[8]

Recipient assessment

Numerous blood tests, body fluid cultures, and chest radiographs are essential preoperative investigations (Table 1). Cardiopulmonary functional assessment includes lung function tests, the 12-minute exercise test, electrocardiography, and echocardiography. Further investigations such as computerised tomography

Table 1. Routine investigations for patients undergoing lung transplantation

Investigation	Recipient assessment	Preoperative investigation	Postoperative monitoring	Out-patient monitoring
Blood tests				
General				
complete blood picture	✓	✓	✓	✓
liver and renal function tests	✓	✓	✓	✓
blood glucose level	✓	✓	✓	✓
clotting profile	✓	✓	as required	
thyroid function test	✓			
Blood grouping, tissue typing, screening for auto-antibodies	✓			
T-cell count		✓	✓	
Cyclosporin level			✓	✓
Serological analysis for				
cytomegalovirus	✓	✓		
herpes simplex virus	✓	✓		
human immunodeficiency virus	✓			
hepatitis B	✓			
hepatitis C	✓			
Epstein-Barr virus		✓		
other viral antibody titre			✓	✓
toxoplasma	✓	✓		
Body fluid cultures				
Urine		✓	✓	✓
Sputum		✓	✓	✓
Nasal swab	✓	✓	✓	
Throat swab	✓	✓	✓	
Radiography				
Chest X-ray	✓	✓	✓	✓

of the thorax, relevant histological examinations, and invasive cardiological studies may be required as indicated. Lung perfusion scanning and/or ventilation scanning are required to determine which lung should be removed from the recipient prior to the SLT. In the event of a marked discrepancy of perfusion results between the two lungs, Griffith et al[9] have recommended that the less perfused side be chosen for transplantation. This choice decreases the need for an intra-operative cardiopulmonary bypass and preserves the remaining function of the native lung in the long term.[9] The time of performing the transplantation is also critical to its success: transplantation should not be undertaken too early such that the attending complications may shorten the patient's life, or so late that the underlying disease progresses to a state that jeopardises the chances of postoperative recovery.

The severity of the illness, as determined by objective measurements (eg spirometry/transfer factor less than one third of the predicted value and a 12-minute walk less than 600 m) can only assess the static components of the disease. A more important determinant is the dynamic component, which is reflected by the rate of deterioration of a patient's condition and the ability to cope with daily activities. These variables can be difficult to assess, and natural fluctuations during the course of the underlying disease must be taken into account. Emotional stability, the amount of social support, and psychological preparation are also essential factors to consider when assessing a patient's eligibility for transplantation.

Donor selection

Matching between the donor and recipient is the next crucial step, especially matching of the blood group and cytomegalovirus (CMV) status. Mismatching of the CMV status increases the chances of postoperative CMV pneumonitis, which is a major cause of death, especially when organs from a CMV-positive individual are donated to a CMV-negative recipient.[10] Full human leukocyte antigen (HLA) typing usually cannot be completed within the short time available for organ procurement, but HLA mismatching has been shown to increase the incidence of obliterative bronchiolitis.[11] Size-matching is also very important: oversized donor lungs predispose to atelectasis and cardiac compression, while undersized organs will become hyperinflated; consequently, both cardiac and pulmonary functions become compromised. The ideal donor lung size—as estimated from age, sex, height, and weight—should be within 20% of the recipient's lung volume.[12] In the same context, if the donor's body weight is less than 75% of that of the recipient, the donor heart may be too small to support the recipient's circulation.[12] The ideal lung or heart-lung transplant is one that (1) has been obtained from a young non-smoker who had not sustained any chest trauma; (2) has not been mechanically ventilated for more than 24 hours immediately prior to transplantation; (3) has minimal bronchial secretions; (4) has minimal evidence of lung collapse; and (5) sustains inflation after manual insufflation with air.

Conditions that absolutely contra-indicate organ donation are blood-borne sepsis, malignancies outside the central nervous system, hepatitis B or C, HIV infection, and direct myocardial toxicity (eg carbon monoxide poisoning). In contrast, relative contra-indications must always be carefully weighed against the potential benefits of transplantation. Such factors include an advanced donor age, a history of smoking, prolonged ventilation, inotrope requirement, and/or high cardiac filling pressures. During the donor organ retrieval, a pulmonary arterial catheter is usually inserted to monitor the fluid status and to maximise cardiac function. If localised consolidation is present in the donor lung, bronchoscopy should be performed to remove any mucous plugs or secretions to see if the consolidation resolves. In the Papworth organ retrieval protocol, the donor's minimal ratio of the arterial oxygen tension (PaO_2) to the fractional inspired oxygen (FIO_2) should be greater than 40 kPa (300 mm Hg). In addition, the minimal left ventricular power should be greater than 0.4 Watts, while inotropes of a dose not more than 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ are given and the left-sided preload is maintained to less than 12 mm Hg.

Procurement of the heart-lung transplant

The surgical technique and principles of organ preservation in heart and lung procurement have been described in detail by Sundaresan et al.[13] Throughout the procurement procedure, the haemodynamic stability of the donor must be maintained by closely monitoring the arterial pressure, central venous pressure, and cardiac rhythm. Excessive fluid administration must be avoided, as the lung graft is extremely susceptible to pulmonary oedema.

Graft preservation plays an important role in ensuring both the early and long-term results of transplantation. Preservation of the heart is achieved by the use of cold (4°C) crystalloid cardioplegia, and that of the lung by flush perfusion with cold modified Euro-Collins solution or University of Wisconsin solution at a dose of 60 mL/kg. To counteract the development

of pulmonary vasoconstriction from the cold stimulation, pretreatment by slowly infusing prostagladin E1 (a potent pulmonary vasodilatator at a dose of 500 μg) into the main pulmonary artery prior to pulmonary flush has been shown to be beneficial.[14,15] Further steps that are essential to ensure graft preservation include the following: (1) adequate decompression of the heart during graft perfusion; (2) maintenance of low perfusion pressure in the pulmonary artery; (3) adequate topical cooling; and (4) minimal and gentle manipulation of donor grafts.

The heart and lung grafts are removed en bloc prior to performing an HLT, or they can be separated and stored if they are to be used in an isolated heart or lung transplantation. The donor graft is completely immersed in cold saline, triple-bagged, and then transported to the site of transplantation in a cold-storage container.

Recipient operations

Aspects of special interest regarding the surgical techniques of HLT and lung transplantation are highlighted below.

Heart-lung transplantation

The standard operative technique of median sternotomy has remained unchanged since the first reported case of HLT at Stanford, United States.[1,16] For patients with prior thoracotomy, however, a bilateral thoracosternotomy 'clamshell' incision is currently used during a DLT. The incision provides better exposure of the posterior and apical pleural adhesions as well as the mediastinal collaterals. All pleural adhesions should be dissected free. Large bronchial arteries and mediastinal collaterals are individually secured with ligatures or hemoclips. Great care should be taken to avoid injury to the phrenic nerves during lung dissection. The patient is then given heparin systemically as well as a standard cardiopulmonary bypass. After a cardiectomy has been performed, the left and right lungs are removed individually.

The graft is prepared by trimming the donor trachea to one cartilaginous ring above the carina. The graft's bronchial secretion should be sent for culture at this stage. The HLT involves performing end-to-end tracheal anastomosis, followed by right atrial and aortic anastomoses. After adequate rewarming, the graft is observed for the return of cardiac activity. If used, the cardiopulmonary bypass can be discontinued, and the heart rate can be maintained at 110 to 120 beats per minute by using an isoproterenol infusion or atrioventricular sequential pacing. Using a positive end-expiratory pressure (PEEP) of 5 cm H_2O, the FIO_2 is gradually adjusted to 0.40, to maintain an arterial oxygen saturation (SaO_2) of greater than 90%.

Single lung transplantation

After selecting the less perfused lung to be transplanted, a pulmonary arterial catheter is inserted and positioned preferably in the contralateral pulmonary artery. The pressures of the pulmonary and systemic arteries, the end-tidal carbon dioxide level, and the SaO_2 are continuously monitored. A Univent tube with a left-bronchial blocker is used for left-lung transplantation, and a left-sided Robertshaw double-lumen tube is used for right-lung transplantation. Cardiopulmonary bypass is made available on standby.

A standard posterolateral thoracotomy is made in the fourth or fifth intercostal space. Haemostasis is maintained while the pleural adhesions and mediastinal collaterals are dissected. At this stage, a trial of causing a temporary occlusion of the pulmonary artery is useful to determine if a partial cardiopulmonary bypass is required. If significant haemodynamic instability ensues, partial cardiopulmonary bypass is instituted using the femoral approach. Bronchial anastomosis is a critical determinant of the success of SLT and DLT, because ischaemia of the donor airway can result in fatal complications such as bronchial dehiscence and late bronchial stenosis. Various techniques have been suggested to improve bronchial healing, such as (1) wrapping the bronchial anastomosis with vascularised tissue (eg a piece of omentum, a pericardial flap, or a pleural flap)[17,18]; (2) telescoping the anastomosis to a depth of one cartilaginous ring[19]; (3) minimising dissection of the recipient airway; and (4) shortening the donor bronchus to within one to two cartilaginous rings of the upper-lobe bronchus. When performing pulmonary artery and vein anastomoses, wide and properly aligned anastomosis is essential. On completing the bronchial and vascular anastomoses, mechanical ventilation of the transplanted lung is started using a 10-cm H_2O PEEP. If ventilation is successful, flexible bronchoscopy is immediately performed to ensure the patency of the tracheobronchial tree and to maintain satisfactory bronchial anastomoses.

Bilateral sequential lung transplantation

Perioperative preparation for a bilateral sequential lung transplantation is similar to that for an SLT. The recipient's surgery entails performing bilateral anterior thoracosternotomy incisions through the fourth or fifth intercostal spaces. The incisions provide superb access to both pleural spaces and the

posterior mediastinum. When removing the native lungs, the left lung can first be isolated and ventilated to allow the complete mobilisation of the right lung, which is reinflated and ventilated; the left lung is then similarly mobilised. A cardiopulmonary bypass is required only if there are problems with the recipient's haemodynamic stability or gas exchange. The right lung is transplanted first and gently inflated after completing the vascular and bronchial anastomoses. Successful ventilation is followed by the transplantation of the left lung. Haemostasis must be achieved before wound closure.

En bloc double lung transplantation

Executing an en bloc DLT by using a tracheal anastomosis is technically more complex than sequential transplantation. Because of the unacceptably high incidence of ischaemic airway complications,[19,20] DLT should not be performed without bronchial artery revascularisation. Compared with the widely used and well-proven bilateral sequential SLT, en bloc DLT is a much less preferred technique.

Living-donor lobar lung transplantation

Living-donor lobar lung transplantation offers a viable and acceptable alternative to children and sometimes adults, when life expectancy is less than a few months and a cadaveric donor cannot be located. The indications, surgical techniques, and intermediate results have been reported in detail by Starnes et al.[21,22] In general, the donor's lower lobe is used as the graft for the corresponding side of the recipient's lung. Occasionally, the middle lobe of the right donor lung is used for a smaller recipient. The early and intermediate results of living-donor lobar transplantation compares favorably to those of cadaveric lung transplantation.[22] Because of the risk to the donor, however, this technique is presently indicated only for patients whose condition rapidly deteriorates.

Perioperative management of transplantation

All blood tests, body fluid cultures, and chest X-rays (Table 1) are repeated for the recipient in the immediate preoperative period. Perioperative immunosuppressive therapy protocols vary among transplantation centres but usually comprise peri-operative azathioprine, methylprednisolone, and either rabbit anti-thymocyte globulin or OKT3 monoclonal antibody to produce rapid immunosuppression.[23] This regimen is followed by standard triple therapy with azathioprine, prednisolone, and cyclosporin as the long-term maintenance drug therapy. Table 2 shows the immunosuppressive protocol currently used for lung transplantation in Hong Kong.

After the transplantation, the patient should be monitored in the intensive care unit. Strict aseptic techniques should be used; and putting the patient in an isolation ward is preferred. To minimise the

Table 2. Immunosuppressive protocol for patients undergoing lung transplantation*

Drug	Dose/route
On arrival to the operating theatre	
Azathioprine	2 mg/kg, intravenous/oral
At induction of anaesthesia	
Methylprednisolone	500 mg, intravenous
At initiation of cardiopulmonary bypass	
Rabbit antithymocyte globulin	0.5 to 1.5 mg/kg in 250 mL normal saline over 10 hours, preceded by oral paracetamol 1 g and intravenous chlorpheniramine 10 mg
During reperfusion of transplanted lung	
Methylprednisolone	500 mg, intravenous
Immediately postoperative	
Methyprednisolone	125 mg, intravenous: three doses (at 8 hr, 16 hr, 24 hr) postoperatively,
Rabbit antithymocyte globulin	at initiation of cardiopulmonary by pass
	2 days of treatment at initiation of cardiopulmonary bypass until target T-cell count <20%, or absolute T cell count <100 cells per mL
Maintenance therapy	
Prednisolone	1 $mg \cdot kg^{-1} \cdot d^{-1}$ (divided into two doses), then gradually reduce to 0.2 $mg \cdot kg^{-1} \cdot d^{-1}$ as maintenance therapy
Azathioprine	2 mg/kg (maximum daily dose), oral, to maintain white blood cell count of >4.5 x 10^9/L
Cyclosporin	10 $mg \cdot kg^{-1} \cdot d^{-1}$ (divided into two doses); adjust dosage according to renal function (aim at cyclosporin trough levels of 300 to 500 μg/L in the first 3 months)

* Heart-lung, double lung, and single lung transplantation

chances of infection, all invasive lines should be removed as soon as the patient is haemodynamically stable. The patient should be weaned from assisted ventilation and then extubated—usually, this can be done within the first day. Sharples et al[24] reported a median postoperative intubation time of 13 hours; patients whose intubation time was longer than 24 hours had a significantly poorer prognosis. Mortality in the first 3 months was reported to be 30% (10/33) for these patients, compared with only 8% (10/33) for patients who were intubated for less than 1 day.[24]

Prophylactic antibiotics are routinely given to all patients in the first few postoperative days to eliminate both Gram-positive and Gram-negative organisms. Antibacterial therapy is subsequently modified according to the culture results of the sputum and other bodily fluids taken intra-operatively from both the donor and recipient. Diuretics should be given to reduce the development of reperfusion pulmonary oedema. Prophylactic ganciclovir is administered to CMV-positive patients for the first 4 weeks after the transplantation,[25] whereas acyclovir is given for the first 3 months to patients who are infected with herpes simplex virus.[26] To treat infection with *Aspergillus* species, a course of itraconazole is started immediately after surgery and continued for several months to years, depending on the estimated risks of recurrent disseminated *Aspergillus* infection in individual patients. Septrin is required for toxoplasma-mismatched patients during the first 4 postoperative weeks.[27] After the fourth postoperative week, septrin (or pentamidine inhalation in the case of septrin intolerance) is routinely administered to all patients as prophylaxis against *Pneumocystis carinii* pneumonia.[28]

Postoperative complications

In the immediate post-transplantation period, haemorrhage and early graft dysfunction are major complications and causes of mortality. Acute rejection, infection, tracheal dehiscence, and graft-versus-host disease occur mainly within the first 3 months. Obliterative bronchiolitis (OB), infection, acute rejection, coronary artery disease, immunosuppressant-related lymphoproliferative disorder, tracheal/bronchial stenosis, and cyclosporin-induced renal failure are common causes of morbidity and mortality thereafter. The more frequent and important problems are discussed below.

Haemorrhage

Sharples et al[24] have reported an increasing risk of early death within the first 3 months of transplantation, with increasing amounts of blood loss in the first 24 postoperative hours. Their study also showed that patients who required a second operation for bleeding also seemed to be at greater risk of early death, although this finding was not statistically significant.[24]

The removal of the recipient's native lung may be accompanied by severe bleeding from the pleura, especially if pleural adhesions are present or if there had been prior pleurodesis or pleurectomy. Bleeding from the posterior pleural space is particularly difficult to control because of the poor visualisation. Severe haemorrhage caused 8% (9/106) and 12% (4/32) of the total mortality in the Pittsburgh and Stanford series, respectively.[9,29] The recently introduced intra-operative use of the antifibrinolytic agent aprotinin to promote pleural haemostasis has, however, significantly reduced postoperative blood loss,[30] and consequently, a history of pleurodesis or pleurectomy is no longer a contraindication to lung transplantation. Whether aprotinin has a benefit to survival cannot as yet be determined, because of the associated confounding factor of altering recipient acceptance criteria.

Early allograft dysfunction

Immediate allograft dysfunction occurs due to the poor preservation or hyperacute rejection of the graft. The dysfunction is manifested as a difficulty in ventilating the transplanted lung and variable degrees of haemodynamic collapse. In contrast, early (in the first 100 days) and late allograft dysfunction are due to acute rejection and OB, respectively. Recent improvements in organ procurement and surgical techniques have helped reduce the mortality from early allograft dysfunction—from 37% in the period 1982 to 1991, to 18% in 1991/1992 in the Pittsburgh series.[9] Because of these encouraging results and because organ donation rates are low worldwide, many transplantation centres have relaxed some of their stringent organ acceptance criteria. It is not known whether these changes will adversely affect the incidence of early allograft dysfunction in the long term.

Infection

Infection continues to be one of the most important causes of morbidity and mortality after transplantation. The incidence of infection is extremely high in the first 3 months and decreases to a relatively stable rate after 1 year, but increases again whenever immunosuppressive drugs are used to treat rejection episodes. In its first 100 HLT patients between 1984 and 1991, the Papworth series reported an average of 0.9 episodes of infection per patient-month in the first month, and 0.4 episodes in the subsequent 2 months.[24] In

Stanford, infection accounted for up to 50% of early deaths (within the first 3 months) and 38% of late deaths; the average number of episodes was 2.74 per patient in 73 heart-lung recipients between 1981 and 1990.[31] In this series, 49% of all infections were bacterial in origin, 14% were fungal, 31% were viral, and 5% were protozoal; less than 2% were caused by *Nocardia* species. Gram-negative organisms accounted for 65% of all bacterial infections, whereas Gram-positive ones caused 27%. *Aspergillus* species and *Candida albicans* were the most common fungal infections, while CMV and herpes simplex virus accounted for the majority of serious viral infections.[31] Bacterial and fungal infections were predominant in the first postoperative month, CMV infection was the most common in the second month, and *Pneumocystis carinii* pneumonia usually occurred between 4 and 6 months after transplantation.[31]

Acute rejection

The onset of acute rejection ranges from a few days to a few years postoperatively. The incidence is highest in the first 3 months and becomes much less significant thereafter. The Papworth series reported an average of 1.7 rejection episodes per patient-month in the first month; the figure fell to 0.5 episodes per patient-month in the subsequent 2 months.[24]

The presentation of acute rejection is non-specific. Symptoms include fever, shortness of breath, chest tightness, decreased exercise tolerance, fatigue, and lethargy; the patient may also report a 10% to 15% reduction in home spirometry performance. It is often difficult to differentiate rejection from infection on clinical or radiological grounds, and fibre-optic bronchoscopy and/or transbronchial biopsies are usually required for a definitive diagnosis.[32] During acute rejection, there is marked perivascular lymphocytic infiltration with or without inflammation of the bron-chioles and large airways, the degree of which is positively correlated with severity. The Papworth series reported that recurrent severe acute rejection appeared to be the most important determinant of the development of OB.[24] A working formulation for the classification and grading of pulmonary rejection[33] is shown in the Box. The standard anti-acute rejection treatment—intravenous pulse methylprednisolone for 3 days, followed by maintenance steroid therapy—is effective in most cases. For recurrent and resistant acute rejection, the administration of rabbit antithymocyte globulin or OKT3 monoclonal antibody may be considered.[34]

Working formulation for classifying and grading pulmonary rejection

Grade A: acute rejection
(I) Minimal acute rejection
(II) Mild acute rejection
(III) Moderate acute rejection
(IV) Severe acute rejection
  (A) Evidence of bronchiolar inflammation
  (B) No evidence of bronchiolar inflammation
  (C) Large airway inflammation
  (D) No bronchioles are present

Grade B: active airway damage without scarring
(I) Lymphocytic bronchitis
(II) Lymphocytic bronchiolitis

Grade C: chronic airway rejection
(I) Bronchiolitis obliterans: subtotal
(II) Bronchiolitis obliterans: total
  (A) Active
  (B) Inactive

Grade D: chronic vascular rejection

Grade E: vasculitis

Obliterative bronchiolitis

Advances in surgical techniques and immunosuppressive treatment have markedly improved early patient survival. The delayed development of OB has now become the most important determinant of the quality of life and long-term survival. The Stanford series has shown that OB develops in 64% of long-term HLT survivors and 68% of SLT or DLT survivors.[35] In the Papworth Hospital, Cambridge, United Kingdom, 86% of all deaths that occurred more than 1 year after the HLT were associated with OB.[36] The precise aetiology of OB has not yet been defined, although 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.[11,37,38]

Obliterative bronchiolitis usually presents with dry unproductive cough, chest tightness, wheezing, and increasing breathlessness. Results from serial lung function tests reveal a combination of severe obstructive and mild restrictive pattern, with minimal disturbance to the lung diffusing capacity. Hypoxaemia develops gradually, as well as hypocapnia rather than hypercapnia (except in the terminal stages of the disease). Obliterative bronchiolitis is pathologically defined as the submucosal scarring of the membranous and respiratory bronchioles and the subsequent eccentric, concentric, or total obliteration of the bronchiolar lumens. Owing to the patchy and focal involvement of the bronchioles, diagnostic rates based on transbronchial lung biopsy results have varied widely, from 15% to 87%.[39,40] Open-lung biopsy may result in higher rates, but its invasive nature limits the role

of this method as a routine diagnostic tool. In 1993, an international working group established a clinical definition for the classification and grading of pulmonary graft dysfunction. The term 'bronchiolitis obliterans syndrome' (BOS) was adopted to connote graft deterioration secondary to chronic rejection. The functional grading of BOS is defined according to the percentage drop in the 1-second forced expiratory volume (FEV_1). Patients with an FEV_1 of at least 80% of the baseline value are graded as having BOS_0; between 66% and 80%, as BOS_1; between 51% and 65%, as BOS_2; and from 0% to 50%, as BOS_3.[41] By retrospectively applying the BOS grading to the Papworth series, it was found that 84% of transplant recipients were free of OB 1 year after transplantation, but only 45% remained OB-free at the end of 5 years.[37] During this period, 85% of patients with BOS_1 had progressed to BOS_2 and 71% of BOS_2 patients had progressed to BOS_3. These results suggested that once BOS_1 develops, most patients will progress to the final stage of disease. The overall median survival time from the initial diagnosis of BOS was reported to be 948 days in this series.[37]

There is currently no effective treatment against OB. The condition, however, may be a manifestation of chronic graft rejection secondary to recurrent acute rejection.[37] And since the early exudative phase of acute rejection is treatable using high-dose oral steroids,[42] the present management of OB focuses on the early detection and early treatment of acute episodes of rejection, as well as more effective maintenance immunosuppression. Although high-dose steroid has been shown to slow the progress of OB, its use is limited by the attending risks of opportunistic infections and other serious side effects. Sharples et al[37] identified the main risk factor for OB development to be three or more acute episodes of graft rejection within the first 6 months after the transplantation. Takao et al[43] have reported the use of nebulised steroids (budesonide 2 mg twice daily) to be effective in decreasing the incidence of acute rejection and exerting a protective effect against OB in patients with recurrent acute rejection, and to have fewer side effects compared with systematic steroids.[43] Regular nebulised steroid therapy may therefore be considered for patients who have more than three episodes of acute rejection within the first 6 months after surgery. Iacono et al[44] have reported aerosolized cyclosporin to be effective against active OB, as demonstrated by the arrest of the deterioration of initial lung function in nine patients who were given such treatment. A large-scale prospective randomised study is currently under way to confirm this beneficial effect.

Alternative immunosuppressive agents may also be useful. One example is FK506, which selectively inhibits the proliferation of T cells by blocking cytokine synthesis. Several studies have shown that FK506 as a maintenance immunosuppressant drug is more effective than cyclosporin in preventing acute rejection and OB.[45,46] Rapamycin inhibits the actions of cytokines and growth factors on T and B lymphocytes and can prevent acute and chronic rejection in animal heart transplantation models.[47,48] By inhibiting the de novo pathway of purine synthesis, mycophenolate mofetil specifically suppresses lymphocyte function and has been shown to be effective in refractory or persistent rejection[49] and chronic rejections of the transplanted heart.[50] These new immunosuppressants are now under trial and may offer new prevention and treatment strategies for OB.

Postoperative monitoring

To monitor the various toxicities associated with immunosuppressant use, chest radiography and blood tests as listed in Table 1 should be performed daily in the early postoperative period. The frequency of testing may be reduced to three times per week once the patient's condition has stabilised. Septic work-up from various sites and viral studies should be conducted at least once a week, or more frequently as clinically indicated. To monitor the return of graft function, daily pocket spirometric measurements (FEV_1 and forced vital capacity) should commence from about 1 week postoperatively.[51] Lung function should be fully tested at 2 to 4 weeks after the transplantation to give baseline measurements and to detect acute rejection and/or infection. Surveillance bronchoscopy is routinely performed on the 10th to 14th postoperative day to assess the integrity of anastomosis, and repeated with transbronchial biopsy at about 4 weeks to obtain a histological baseline. If there are no complications, most patients can be safely discharged home at about 4 weeks after the transplantation.

Follow-up

Patients should monitor their body weight, temperature, and spirometry daily at home. They should report all symptoms and any reduction in spirometric readings of 10% to 15% below baseline values. Whenever indicated, diagnostic fibre-optic bronchoscopy can be used to differentiate between infection and rejection. Specimens for virological (ie CMV, herpes simplex virus, and Epstein-Barr virus) and microbiological (bacterial smear and culture, acid-fast

Table 3. Details of lung and heart-lung transplant recipients in Hong Kong

Patient	Sex	Age (years)	Preoperative diagnosis	Operation/date	Complication	Current status (Aug 1999)
1	F	27	Lymphangio-leiomyomatosis	SLT*/July 1995	Infection, acute rejection, obliterative bronchiolitis	Alive, BOS_2†
2	F	37	Eisenmenger's syndrome	HLT‡/Dec 1995	Fulminant fungaemia marrow failure, graft-versus-host disease	Died within 2 months of transplantation
3	F	33	Bronchiectasis	DLT§/May 1997	Infection	Alive, BOS_0
4	F	37	Tuberous sclerosis	SLT/May 1998	Infection	Alive, BOS_0
5	F	35	Lymphangio-leiomyomatosis	DLT/Apr 1999	Infection	Alive

* SLT single lung transplantation
† BOS bronchiolitis obliterans syndrome
‡ HLT heart-lung transplantation
§ DLT double lung transplantation

bacilli, fungus, and *Pneumocystis carinii* pneumonia) testing should be obtained from bronchoalveolar lavage of different lung segments. In addition, at least five pieces of transbronchial biopsy from different lung segments on one side, each containing at least some bronchioles and more than 100 air sacs,[52] should be sent for histological examination. Routine surveillance bronchoscopy during follow-up is not recommended, because no definite benefits have been identified.[53]

A chest X-ray, full pulmonary function tests, and routine blood tests must be performed during each follow-up visit. Any radiographic or functional changes should call for closer follow-up, and adjustments to immnuosuppressive therapy should be made whenever necessary. During the gradual recovery of allograft function, the patient's well-being, exercise tolerance, and lung function will continue to improve until a plateau is reached. At about 6 to 12 months post-transplantation, approximately 50% and 90% of the predicted FEV_1 can be achieved in SLT[54] and HLT[55] patients, respectively.

Local experience of lung transplantation

In July 1995, the first SLT was sucessfully performed in Hong Kong for a young Chinese woman who had end-stage lymphangioleiomyomatosis. Two DLTs, and another SLT followed in the subsequent 4 years. All four patients are still surviving, and the survival time for the first SLT patient is already more than 4 years. The HLT patient unfortunately died within 2 months of the transplantation from fulminant fungaemia secondary to marrow failure and graft-versus-host disease. Details of the local lung and heart-lung transplant recipients are shown in Table 3. As of August 1999, there are two patients on the waiting-list for an HLT and two for a DLT.

Conclusion

Lung transplantation is an invaluable treatment modality for many patients suffering from end-stage lung disease. Due to the marked shortage of organ supply worldwide, however, about 20% to 25% of the patients who are on the waiting-list for transplantation die from their disease while waiting for the availability of donor organs.[56,57] Since 1990, living-donor lobar lung transplantation has been attempted in a few transplantation centres in the United States, and preliminary results have been encouraging.[22] Nevertheless, ethical concerns need to be explored before this method can be widely adopted.

It is important and indeed urgent for the medical profession to publicise transplantation as an effective and viable treatment option in appropriate cases, and to enhance public awareness as to the need for organ donation.

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