Review Article

Perioperative anaesthetic considerations for patients undergoing lung transplantation

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Purpose: Five thousand, two hundred and eight lung transplants were performed worldwide before April, 1996. This review will discuss lung transplantation from an historical perspective, its indications, donor and recipient selection criteria, donor lung preparation, surgical considerations, perioperative anaesthetic management, and associated morbidity and mortality.

Source: Recent literature on perioperative anaesthetic management of lung transplantation and experience from international centres including the Toronto Lung Transplant Group and the St. Louis Lung Transplant Group.

Principal findings: Lung transplantation comprises of a family of operations, including single lung transplant, bilateral single lung transplant, lobar transplant and block heart-lung transplant. Improved donor lung preservation techniques have increased the duration of cold ischaemic time. The advent of bilateral single lung transplant has decreased the requirement for cardiopulmonary bypass, and airway complications have been reduced by adoption of the telescoping bronchial anastomoses. Advances in perioperative monitoring (including transoesophageal echocardiography), pulmonary vasodilators (e.g., nitric oxide and prostaglandin E₁), cardiopulmonary bypass and ventilatory management, and a better understanding of the pathophysiological processes during the procedure have improved perioperative anaesthetic management. Also, advances in broad spectrum antibiotics and immunosuppressant drugs have improved the outcome by better management of the complications of infection and rejection.

Conclusion: Lung transplantation improves the quality of life with marginal improvement in life expectancy of the recipients. It is an expensive procedure requiring continued resources for long term management of these patients.

Objectif : Jusqu'en avril 1996, cinq mille, deux cent huit transplantations de poumons avaient déjà été effectuées à travers le monde. Ce survol permettra de discuter de la transplantation pulmonaire dans sa perspective historique, ses indications, les critères de sélection du receveur et du donneur, la préparation du poumon du donneur, les considérations chirurgicales, la gestion périopératoire de l'anesthésie et la mortalité et la morbidité associées.

Source : Les publications récentes traitant de la gestion périopératoire de la transplantation pulmonaire et de l'expérience acquise par des centres internationaux dont le *Toronto Lung Transplant Group* et le *St. Louis Lung Transplant Group*.

Principales constatations : La transplantation pulmonaire englobe une famille d'interventions dont la transplantation unipulmonaire, bilatérale simple, lobaire et coeur-poumons en bloc. L'amélioration des techniques de préservation des poumons du donneur a permis l'amélioration de la durée de l'ischémie froide. L'avènement de la transplantation bilatérale simple a réduit la nécessité de la circulation extracorporelle et l'introduction des anastomoses télescopiques a permis de réduire les complications particulières aux voies aériennes. Le perfectionnement du monitoring périopératoire (dont l'échographie transoesophagienne), des vasodilatateurs pulmonaires (par ex., l'oxyde nitrique et la prostaglandine E₁), de la gestion de la circulation extracorporelle et de la ventilation, et une meilleure connaissance du processus physiopathologique propre à l'intervention ont permis d'améliorer la conduite anesthésique périopératoire. Également, les progrès réalisés dans l'antibiothérapie à large spectre autorisent un pronostic plus favorable grâce à un meilleur contrôle de l'infection et du rejet.

Conclusion : La transplantation pulmonaire améliore considérablement la qualité de vie mais marginalement l'expectative vitale. Elle coûte cher et requiert des ressources continues pour la prise en charge à long terme des transplantés.

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LUNG transplantation has gained acceptance as a viable surgical procedure during the last decade for patients with end-stage lung disease (ESLD). Data from the St. Louis International Lung Transplant Registry show a total of 5208 lung transplants performed before April 1, 1996. Of these, 3145 were single lung transplants (SLTs), 1809 bilateral/sequential single lung transplants (BSLTs), and 243 en-bloc double lung transplants (DLTs).¹ Of the 200 paediatric transplants performed before April 1, 1996, 36 were SLTs, 146 were BSLTs, and 17 were DLTs.¹ Despite the progressively increasing number of lung transplants performed each year, the number of recipients awaiting lung transplants has increased.² In contrast, the number of heart-lung transplants (HLTs) performed each year has declined with the introduction of SLTs and BSLTs.²

Historical perspective

In 1963, James Hardy performed the first human lung transplant in a 58-yr-old patient with bronchogenic carcinoma.³ Although the patient survived for only 18 days, the technical and functional feasibility of this procedure stimulated an international interest in lung transplantation. Unfortunately, a majority of the initial recipients experienced either early rejection or bronchial dehiscence, longest survival being eight months.⁴ This poor outlook began to change in 1983 when the Toronto Lung Transplant Group performed the first successful SLT utilizing omental wrapping around the bronchial anastomosis in a patient with severe idiopathic pulmonary fibrosis.⁵ Subsequently, DLTs, HLTs and BSLTs were introduced into clinical practice.

Choice of operation

The pathology in patients with ESLD for lung transplantation includes obstructive lung disease (chronic obstructive pulmonary disease), restrictive lung disease (pulmonary fibrosis), infectious lung disease (cystic fibrosis) and pulmonary vascular disease (pulmonary hypertension).

Chronic obstructive pulmonary disease (COPD) is the most common indication for performing lung transplant.¹ Others are listed in Table I.¹ Single lung transplant, initially restricted to patients with end-stage pulmonary fibrosis, has now been performed successfully in patients with COPD, primary pulmonary hypertension, and Eisenmenger's syndrome.⁶⁻⁸ Fibrotic lung disease is considered an ideal indication for SLT as both the ventilation and perfusion are distributed preferentially to the transplanted lung which is more compliant and has lower pulmonary vascular resistance (PVR).⁹

Single lung transplant, bilateral single lung transplant and heart-lung transplant can be performed for pulmonary hypertension. Improvement in right ventricular (RV) structure and function after SLT for

TABLE 1 Indications for Lung Transplants by Diagnosis¹

Indication	%/n (Total) *
Chronic Obstructive Pulmonary Disease (COPD)	39%
Idiopathic Pulmonary Fibrosis (IPF)	16%
Cystic Fibrosis (CF)	14%
Primary Pulmonary Hypertension (PPH)	7%
Bronchiectasis	3%
Retransplantation	3%
Eisenmenger's Disease	2%
Bronchiolitis Obliterans (BO)	2%
Other (specified)	10%
Other (unspecified)	4%

*Values are percentage of total number (n=5208)

primary pulmonary hypertension has been demonstrated by 2-D and Doppler echocardiography in a series of 14 patients.⁷ The RV dimensions decreased and ejection fraction increased in all the patients in the early post-transplant period (<three months). A later follow up (six months to two years) of 12 patients demonstrated decrease in right ventricular wall thickness in 10 patients.⁷ However, SLT for pulmonary hypertension is characterized by a high incidence of early (reperfusion injury) and late complications (V/Q mismatch).¹⁰ Bando *et al.* demonstrated higher mortality, prolonged ICU stay, and less symptomatic improvement following SLT in a series of 48 pulmonary hypertension recipients.¹⁰ Therefore, despite a shortage of donor organs, SLT may not be the procedure of choice for patients with pulmonary hypertension, and outcome studies comparing SLT and BSLT for pulmonary hypertension are needed.

Bilateral single lung transplant is considered the procedure of choice for cystic fibrosis and bronchiectasis to prevent the spread of infection from the native into the transplanted lung. However, SLT has been successful in these patients.¹¹ Cystic fibrosis is the most common indication for paediatric lung transplantation (Table II).¹ Current indications for HLT are limited to patients with congenital heart disease and/or left ventricular dysfunction with associated pulmonary disease. Heart-lung transplant is associated with an increased incidence of graft rejection or obliterative bronchiolitis (OB), development of accelerated coronary artery disease and complications related to cardiopulmonary bypass (CPB).¹²

Recipient selection

Although selection criteria may vary between centres, patients generally have irreversible and progressive pulmonary disease requiring O₂ therapy and an anticipated life expectancy <18 mo.^{6,13} The upper age limit for recipients varies as biological rather than chronological age is of more importance. Recipients >60 yr have been accepted in the absence of other complications.¹⁴ In

patients with systemic disease with pulmonary manifestations, selection should be confined to those with pathology principally in the lungs.¹³ Renal or hepatic insufficiency is a contraindication as adverse effects of immunosuppressive agents may exacerbate renal or hepatic impairment. Although multi-organ failure has been considered a contraindication to transplantation, multi-organ transplants have been performed.¹⁴ Malignancy is a contraindication because of the risk of reactivation with immunosuppression. In the presence of malignancy, the disease-free interval before transplantation varies according to the primary site and should be considered individually in each patient.¹⁴

The nutritional status of the recipients should be adequate: severe cachexia and morbid obesity are contraindications.¹⁴ Smokers should be free from smoking for 6–12 mo before transplantation.¹⁴ A recipient should also exhibit a stable psychosocial profile without alcohol or drug dependence. Major psychiatric illness is usually considered a contraindication.¹⁴

Dependence on corticosteroids was considered a contraindication to pulmonary transplantation. Patients were required to discontinue steroid therapy before surgery as steroids were presumed to inhibit healing of the airway anastomosis.¹⁵ However, patients receiving perioperative steroids have undergone successful transplantation without increased anastomotic or wound complications.⁶ Early use of corticosteroids in the posttransplant period may benefit some patients by improving bronchial healing and reducing the incidence of stenotic complications.⁶ Schafers *et al.* did not find increased morbidity or mortality following lung transplantation in patients receiving preoperative prednisone up to 0.3 mg·kg⁻¹·day⁻¹.¹⁶ Patients receiving preoperative prednisone should be able to tolerate a reduction in the dose to 15 mg·day⁻¹ before transplantation.¹⁴

Ventilator-dependent patients were considered unsuitable candidates for transplantation because of the risk of airway colonization leading to nosocomial infections, and accompanying muscle deconditioning and multi-organ failure.¹⁴ However, carefully selected patients have been transplanted successfully without increased postoperative morbidity or mortality. In a series of 10 ventilator-dependent patients, the postoperative course and infectious and rejection complications were similar to those of spontaneously breathing patients undergoing lung transplantation.¹⁷ In another series of patients undergoing DLT, pretransplantation ventilation did not prolong the posttransplantation hospital stay of these patients.¹⁸ Recently, patients treated with extracorporeal membrane oxygenation have also undergone successful lung transplantation.¹⁹

TABLE 2 Indications for Paediatric Transplants by Diagnosis¹

Indication	%/n (Total) *
Cystic Fibrosis (CF)	46%
Primary Pulmonary Hypertension (PPH)	15%
Idiopathic Pulmonary Fibrosis (IPF)	7%
Bronchiolitis Obliterans (BO)	5%
Retransplantation	5%
Eisenmenger's Disease	5%
Other	17%

*Values are percentage of total number (n=200)

Preoperative evaluation

Upon satisfying the recipient selection criteria, thorough history, physical examination and laboratory studies are performed. These patients frequently are oxygen dependent and severely limited in their mobility and ability to perform even the routine tasks of daily living.¹³ Preoperative assessment is directed to ascertain right and left ventricular function, presence or absence of pulmonary hypertension, degree of obstructive airway disease, exercise tolerance, and other major organ system functions. Evaluation includes a battery of pulmonary function testing, cardiac evaluation, and haematological, biochemical and immunological studies.

Pulmonary testing at our institution includes exercise tolerance (a treadmill walking protocol), pulmonary function tests with DLCO and ABG, chest CT without contrast, and quantitative V/Q scan if indicated. Cardiac studies include 2-D echocardiogram with Doppler estimation of pulmonary artery pressure, multiple uptake gated acquisition scan and cardiac catheterization to determine right and left ventricular function. Coronary angiography may be performed even in asymptomatic patients >45 yr with negative non-invasive testing.¹⁴ Routine angiography for exclusion of asymptomatic coronary artery disease (CAD) in patients with a history of smoking has not been shown to be justified. Patients identified as high risk by the presence of additional CAD risk factors may benefit from coronary angiography.²⁰ Right ventricular function can be compromised by ESLD. Right ventricular ejection fraction (RVEF) <20% may be considered the lowest acceptable limit for successful transplantation.⁹ This lower acceptable limit of preoperable RV function is somewhat arbitrary since improvement in RV function has been reported following lung transplantation.⁷ As echocardiographic examination for assessment of RV size or function may be suboptimal, techniques such as ultrafast CT has been suggested as an alternative for quantitative assessment of ventricular volume and function for preoperative evaluation.²¹ In patients with pulmonary hypertension, preoperative transoesophageal echocardiography (TEE) has been shown to provide additional diagnostic information undetected by right and left heart catheterization, transthoracic echocardiography, or radionuclide ventriculography. The additional information obtained [proximal pulmonary artery emboli (three), patent foramen ovale with right to left shunting (two), atrial septal defect (two), double-outlet right ventricle (two), ventricular septal defect (two), and exclusion of atrial septal defect (one)] altered the assignment of surgical therapy in 25% of patients with pulmonary hypertension evaluated for lung transplantation in one series.²²

Haematological and biochemical screening is performed to assess other organ system function. A Mantoux skin test detects previous tuberculosis exposure and immunological screening determines ABO group, human-immunodeficiency virus (HIV) serology, hepatitis B surface antigen (HBsAg) and cytomegalovirus (CMV) status.¹⁴ Recipients with positive HIV serology are unsuitable for lung transplantation due to increased risk from added immunosuppression.

Donor selection

Despite the shortage of donor lungs, only lungs from suitable perfused organ donors are accepted for transplantation as status of the implanted lung is one of the important predictors of outcome.⁶ The majority of donors are victims of gunshot wounds (31%), intracranial haemorrhage (24%), and motor vehicle accidents (21%).¹ Only 5–10% of perfused organ donors have lungs acceptable for transplantation, as either direct (trauma-related) or indirect (aspiration, infection, neurogenic pulmonary oedema) injuries render them unsuitable for transplantation.²³ Pulmonary “twinning” or the use of one donor lung block for SLTs in two recipients has increased the donor lung pool and lowered the cost of retrieval per lung.²⁴ In urgent situations, such as in infants requiring extracorporeal membrane oxygenation, lobar transplantation (living related or cadaveric) is an alternative in the environment of donor lung shortage.²⁵ Also, bilateral lobar transplantation may be an option for patients with cystic fibrosis and life-threatening respiratory decompensation.²⁵

The majority of suitable donors are <55 yr without pulmonary trauma or severe preexisting lung disease.^{26,27} Serial chest X-rays should be free from acute or chronic parenchymal lung disease.²⁶ Bronchoscopic examination including Gram's stain of the bronchial washings should be normal.²⁶ Some centres accept donors up to 60 yr, and a smoking history is acceptable unless the donor has chronic obstructive pulmonary disease or pulmonary fibrosis.^{27,28} Oxygenation should be satisfactory, i.e., $\text{PaO}_2 > 300$ mmHg breathing FiO_2 1.0 with 5 mmHg PEEP or $\text{PaO}_2 > 100$ mmHg with FiO_2 0.4.^{26,28} Donor lungs are matched with recipients within the same ABO group.²⁶ Human leukocyte antigen (HLA) matching is not performed because the lungs can deteriorate during the time required for matching and HLA matching has not been shown to correlate with the frequency of chronic rejection.²⁹ Where possible, CMV serology should be negative or identical to that of the recipient.³⁰ However, recent data from the St. Louis International Lung Transplant Registry failed to demonstrate survival advantage at one and two years posttransplantation by avoiding

donor-recipient CMV mismatching. Positive HIV antibody or HBsAg excludes a patient as a donor.²⁶

Size matching is done by comparing the predicted lung volumes (total lung capacity and forced vital capacity) of the potential donor and recipient calculated by established formulas based on height, age and sex.^{23,29} Vertical and horizontal radiographic chest measurements of the donor and prospective recipients for size matching may be less reliable and should not be primary considerations for size matching.^{26,29} Recipients with obstructive lung disease tolerate undersized donor lungs better than oversized donor lungs which can cause pulmonary atelectasis and cardiac compression.²⁷ Recipients with pulmonary fibrosis may receive a lung larger than the native lung because the mediastinum shifts and the thorax expands to accommodate the transplanted lung.^{27,29} In patients with pulmonary hypertension, a donor lung of comparable size to the recipient is usually transplanted.²⁷ Undersized lungs should be avoided in patients with septic lung disease because of the potential for postoperative pleural space infection.²⁶ For double lung recipients, an effort is made to avoid oversized donor lungs to facilitate chest closure.²⁷

Donor lung preparation

Viability of the ischaemic harvested lungs has been extended by the use of cryopreservation methods. With optimal preservation techniques, ischaemic times up to nine hours can be tolerated without severe deterioration in outcome, although it has been suggested that preservation time be kept under three hours.³¹ Reliable pulmonary allograft function and survival after 12–18 hr ischaemia have been achieved in several animal species using hypothermic perfusion with flush solutions with or without pretreatment with prostaglandins.^{32,33} Addition of a variety of oxygen-free radical scavengers including dimethylthiourea, as well as a modification of the reperfusion environment by leukocyte depletion techniques improve lung-graft function in a variety of experimental models.^{34,35}

The method of human lung preservation varies among different transplant centres. The Washington University Lung Transplant Group technique involves systemic heparinization followed by administration of prostacyclin, 500 µg, directly into the main pulmonary artery (PA) prior to pulmonoplegia at 4°C through a large bore cannula.²⁷ After gross inspection and palpation *in situ*, lungs are harvested following administration of a cold flush of Euro-Collins or University of Wisconsin solution into the PA. The University of Wisconsin solution in combination with prostacyclin donor pre-treatment may provide superi-

or postoperative oxygenation to donor core cooling or Euro-Collins solution.³⁶

During harvest, a cuff of left atrium is removed with donor pulmonary veins to facilitate anastomosis to the recipient left atrium. Ventilation is continued with 100% oxygen until tracheal clamping and the lungs are removed en-bloc, with main bronchus and pulmonary artery, and inflated to approximately $\frac{2}{3}$ of total lung capacity. Hyperinflation of the lungs before harvest and during storage improves PaO₂ and early posttransplantation lung function in canine experimental models.³⁷

Surgical considerations

Posterolateral thoracotomy is performed for SLT, whereas bilateral antero-thoracosternotomy is performed for BSLT. Infrequently, CPB is required for patients undergoing SLT or BSLT except for patients with pulmonary hypertension. The lung with the poorer perfusion is preferentially transplanted for SLT. Similarly, the less perfused lung is transplanted first during BSLT. Transplantation of the right lung may be preferred for patients with COPD as unimpeded caudad movement of the hyperinflated native lung causes less mediastinal shift and compression of the transplanted lung. The sidedness of lung transplantation also depends upon surgical considerations related to the lengths of pulmonary veins and bronchi on each side.

Double lung transplant is of only historical interest.^{12,38,39} Bilateral single lung transplant avoids some of the complications of DLT.^{39,40} Ischaemic complications of the airway have been reduced by adoption of the bilateral main-stem bronchial anastomoses.³⁹

Disruption of the airway anastomosis limited success of early lung transplants but newer surgical techniques have improved healing of the airway anastomoses.^{39,41} Reinforcement of the end-to-end bronchial anastomosis with omental wrap is no longer routinely performed for prevention of bronchial dehiscence. This procedure aided anastomotic revascularization by bringing an intact blood supply around the anastomosis. Instead, a telescoping technique of intussuscepting one or two cartilaginous rings of smaller into larger bronchus is often employed.^{6,41} This technique was initially developed to enhance the blood supply of the bronchial anastomosis in a canine lung transplantation model by Veith and Richards,⁴² and later applied clinically by the San Antonio Lung Transplant Group.⁶ In a series of 47 patients undergoing lung transplantation, 39 underwent end-to-end bronchial anastomosis with omentopexy, and of these, six had partial or complete airway dehiscence. Of the remaining eight patients who underwent

a telescoping technique with perioperative corticosteroid administration, only one developed bronchomalacia.³⁹

Preoperative and intraoperative anaesthetic management

Anaesthetic management requires preoperative evaluation and preparation within the limited time, considerable OR resources and manpower, judicious cardiopulmonary interventions and effective communication and organization among the members of the transplant team.

Preoperative preparation and monitoring

Preoperative considerations include airway evaluation, NPO status, oxygen and steroid dependency, pulmonary and cardiac status, and any deterioration in the clinical condition since the last visit. Preoperative immunosuppression protocols vary: one comprises preoperative administration of 5 mg.kg⁻¹ cyclosporine *po*, and 2 mg.kg⁻¹ azathioprine *iv*.⁴³ Bronchodilator therapy is continued until surgery and antibiotics are administered *iv* during the immediate preoperative period. Anxiolytic or sedative premedication (e.g., midazolam *iv*, propranolol *po*, or morphine *im*) may be beneficial for patients with primary pulmonary hypertension by ameliorating any increase in PVR and RV afterload associated with anxiety.⁴⁴ In patients with COPD, sedative premedication, especially with opioids, can lead to respiratory compromise by aggravating preexisting hypoxia and hypercarbia and should be avoided.⁴⁴ In patients with cystic fibrosis, sedative premedication should be administered carefully to avoid respiratory compromise. Chronically cyanotic patients with severe polycythaemia may benefit from phlebotomy and haemodilution as prophylaxis against clotting derangements.⁴⁵

Because of the possibility of severe cardiopulmonary instability during one lung ventilation (OLV) and PA clamping, continuous PA catheter and invasive blood pressure monitoring is usually employed. The PA catheter generally floats to the lung with preferential perfusion. During surgery, the PA catheter is palpated prior to PA stapling to make sure that the catheter is not in PA of the operative lung and, if necessary, the PA catheter is withdrawn and refloats to the non-operative lung. The pulmonary capillary wedge pressure (PCWP) must be interpreted with caution in association with pneumonectomy as spuriously low readings may be obtained.⁴⁶ Routine use of transoesophageal echocardiography (TEE) monitoring has been recommended during lung transplantation.⁴⁷ Transoesophageal echocardiography can assist the intraoperative management by diagnosing RV dys-

function, hypovolaemia, outflow tract obstruction, patent foramen ovale, and direction of intracardiac shunts besides providing additional functional and morphological information.^{22,48,49} Intraoperative TEE monitoring may avoid unnecessary institution of CPB in these patients by assisting the correct diagnosis of haemodynamic dysfunction.⁴⁷

Induction and maintenance of anaesthesia

Special considerations during induction of anaesthesia include the potential for regurgitation and aspiration, reactive airway disease, and haemodynamic instability secondary to poor ventricular function. After preoxygenation, intubation is usually performed using a modified rapid-sequence induction technique.^{38,44} Either a standard left or right-sided double-lumen tube (DLT) or a combination single-lumen endotracheal tube with endobronchial blocker (e.g., Phycon Univent tube) is used for OLV. Alternatively, a single-lumen endotracheal tube and a bronchial blocker (Fogarty occlusion catheter) can be placed under direct vision with a bronchoscope. A left-sided DLT is preferred to a right-sided tube where feasible to avoid the impaired ventilation of the right upper lobe. The right-sided DLT can also interfere with right-sided bronchial anastomosis. During BSLT, the endobronchial lumen of DLT can be retracted at the time of bronchial transection of the second lung while continuing ventilation of the first transplanted lung. During use of a combination single-lumen endotracheal tube with an endobronchial blocker for BSLT, the endobronchial blocker of the tube is withdrawn into the trachea after transplantation of the first lung and repositioned into the main-stem bronchus of the second lung under direct vision with a fiberoptic bronchoscope.⁵⁰ A nasogastric tube is inserted after intubation of the trachea, but suction is initially avoided to prevent removal of intragastric cyclosporine.³⁸ Hypotension following induction of anaesthesia is frequently encountered due to tamponade secondary to over-distension of the lungs and impaired venous return, diminished RV output as a consequence of increased PVR, withdrawal of high resting catecholamines, and/or direct cardiovascular depressant effects of anaesthetic drugs.^{38,44} Treatment of hypotension following induction of anaesthesia depends upon its aetiology and is usually directed towards maintenance of chronotropic and inotropic action of the heart, optimization of preload and afterload (including both PVR and systemic vascular resistance) and reduction of the intrathoracic pressure. Anaesthesia is maintained using oxygen with or without air, opioids, non-depolarizing muscle relaxants, and benzodiazepines and/or low concentrations of inhalational agents. Low concentrations of inhalational

agents can be used safely during maintenance of OLV without increasing the risk of additional intrapulmonary shunting.⁵¹

Special intraoperative considerations

Following institution of OLV, the effects on airway pressure, oxygenation, and haemodynamic variables are assessed. Ventilation is usually performed with a volume cycled ventilator using tidal volumes of approx. 10 ml·kg⁻¹ and inspired oxygen adjusted to maintain adequate arterial oxygenation. Patients with restrictive lung disease often require small tidal volumes and fast respiratory rate, whereas those with obstructive lung disease require prolonged expiratory periods to minimize air trapping. Some form of differential lung ventilation (continuous positive airway pressure or oxygen insufflation to the non-ventilated lung) may at times be necessary to minimize intrapulmonary shunting during OLV.⁵² Some patients undergoing lung transplantation develop cardiac or respiratory instability during the procedure requiring CPB. Instability may be caused by either inadequate ventilation or oxygenation especially during OLV or acute RV failure following clamping of the PA artery. Cardiopulmonary instability can also develop due to hyperinflation of the lungs (air trapping) in patients with obstructive lung disease leading to decreased venous return, cardiac output, and systemic hypotension.⁵³ Air trapping is not a clinical problem in patients with pulmonary fibrosis undergoing SLT.⁴⁸ Permissive hypercapnia or deliberate hypoventilation has been employed successfully in patients with COPD.⁵⁴ Deliberate hypoventilation can ameliorate the haemodynamic instability induced by air trapping and may obviate the need for CPB during lung transplantation in patients with severe obstruction to expiratory flow. However, marked acidemia can become a limiting factor in such situations.

Right ventricular failure and hypotension can be a considerable problem upon PA clamping. Patients with restrictive lung disease frequently require RV unloading with pulmonary vasodilators as PVR often increases considerably on PA clamping. Prostaglandin E₁ (PGE₁) infusion, 4–12 ng·kg⁻¹·min⁻¹ *iv*, for pulmonary vasodilatation leads to concomitant systemic vasodilatation and arterial hypotension, and may worsen oxygenation due to increased intrapulmonary shunting.^{55,56} Prostaglandin E₁ infusion during the perioperative period may require concomitant administration of vasopressors to maintain normotension.⁵⁶ Inhaled nitric oxide (NO), 40–60 ppm, in contrast to PGE₁ *iv*, causes selective pulmonary vasodilatation without affecting systemic vasculature and mean arterial pressure^{55,56} and may also improve oxygenation in

SLT recipients without pulmonary hypertension who have early postoperative pulmonary dysfunction (PaO₂/FiO₂ <160).⁵⁵ Nitric oxide may be the drug of choice for treatment of pulmonary hypertension and/or right ventricular failure associated with systemic arterial hypotension.⁵⁶

It is important to identify patients requiring CPB prospectively to avoid deleterious trials of OLV or PA clamping.⁵⁷ Poor RV function and pulmonary hypertension have been identified as predictors of the need for intraoperative CPB in children.⁵⁸ Patients with obstructive lung disease rarely require CPB compared with patients with restrictive lung disease.^{57,59} According to de Hoyas *et al.*, the requirement for intraoperative CPB can be predicted from preoperative cardiopulmonary performance in SLT recipients for restrictive lung disease.⁵⁷ Although no single preoperative predictor consistently identified patients requiring CPB, the combination of a six-minute walk <300 m, an exercise RVEF <27%, treadmill exercise (1 mph, 4% gradient) SaO₂ <85% with O₂ supplementation, and VO₂ >5 L·min⁻¹ during exercise successfully identified the patients requiring CPB.⁵⁷ de Hoyas *et al.* found that preoperative cardiopulmonary performance correlated with intraoperative haemodynamic changes necessitating CPB.⁵⁷ During trial of PA clamping, patients requiring CPB responded with a 31% reduction in cardiac index and increases in PVR and alveolar-arterial O₂ gradient.⁵⁷ Similarly, baseline PA pressures, PVR and alveolar-arterial O₂ gradient were higher (45 ± 4 mmHg, 447 ± 56 dyne·sec·cm⁻⁵ and 443 ± 44 mmHg, respectively) in patients with restrictive lung disease requiring CPB.⁵⁷ Hirt *et al.* noted a decrease in cardiac index <1.5 L·min⁻¹ and a concomitant rise in PVR from 434 ± 148 to 1188 ± 235 dyne·sec⁻¹·cm⁻⁵ upon PA clamping in patients requiring CPB during SLT for pulmonary fibrosis.⁵⁹ No preoperative predictors for intraoperative CPB could be identified in adults by Triantafyllou *et al.*⁶⁰ They found that 61% of patients required CPB in a series of 18 patients who developed donor lung dysfunction manifested by increased PA pressure, decreased lung compliance and pulmonary oedema after reperfusion of the first donor lung during BSLT.⁶⁰

After implantation, perfusion and ventilation of the implanted lung are begun simultaneously. Positive end expiratory pressure (5–10 cmH₂O) is usually added to allow adequate oxygenation with a low FiO₂ and to minimize alveolar transudation. Frequently, a transplanted lung exhibits “pulmonary reimplantation response” manifested as low pressure pulmonary oedema with poor lung compliance and oxygenation.⁶¹ Pulmonary reimplantation response (PRR) is probably

the result of preservation ischaemia-reperfusion lung injury, but may also be related to denervation and loss of lymphatic drainage of the transplanted lung.⁶¹ Shorter ischaemic times and improved donor lung preservation with glutathione containing solutions may lessen the severity of the reperfusion injury.^{61,62} Administration of a prostaglandin I_2 analogue (OP41483 α CD) immediately before and after reperfusion can prevent the reperfusion injury by inhibition of hydroxyl ($OH^\cdot$) free radicals generation and microemboli formation.⁶³ Rarely, reimplantation response may be accompanied by pulmonary hypertension.⁴⁵ Prostaglandin E_1 infusion, $0.05 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, or inhalation of nitric oxide, 40–80 ppm, can be beneficial in these patients.⁴⁵

Postoperative management

Optimal management of ventilation, haemodynamics and pain; prevention and treatment of infection, and institution of an optimal immunosuppression regimen are of prime importance in the early postoperative period.

Ventilatory management

At the end of the surgical procedure, the double lumen tube is usually changed to a single lumen tube. The goals of ventilatory management are to achieve the lowest possible fraction of inspired oxygen compatible with adequate oxygenation and to minimize peak airway pressures.⁶⁴ A combination of diuresis, PEEP, and low tidal volumes usually achieves the desired result.⁶⁴ Bronchial anastomotic damage as well as haemodynamic embarrassment is minimized by limiting the peak airway pressures to $<40 \text{ cmH}_2\text{O}$.

Ventilatory management depends on the type of the transplant performed (SLT *vs* BSLT) and the underlying disease process. Five to ten mmHg of PEEP are routinely employed following SLT and BSLT except in patients with obstructive lung disease treated with SLT.

SINGLE LUNG TRANSPLANT

Obstructive lung disease: Positive end expiratory pressure is avoided and lower tidal volumes are used to limit overexpansion of the native lung. Preferential ventilation of the more compliant native lung can be treated with independent lung ventilation using a double-lumen endobronchial tube.⁵³ In most patients with COPD, the trachea can be extubated in three days.

Restrictive lung disease: Patients with restrictive lung disease usually require prolonged ventilatory support compared with patients with obstructive lung disease.

Duration of postoperative ventilatory support reported by the Toronto Lung Transplant Group ranged from 3–10 days (mean 5.5 days) in a small series of patients undergoing SLT for pulmonary fibrosis.⁹

Pulmonary vascular disease: In patients with pulmonary hypertension treated with SLT, 90–95% of the cardiac output is diverted through the transplanted lung.⁶⁵ Heavy sedation is essential during ventilation for the first 48–72 hr to prevent the pulmonary hypertensive crises.⁶⁵

BILATERAL SINGLE LUNG TRANSPLANT

Prolonged ischaemia of the second transplanted lung can increase the risk of PRR in these patients.

Mechanical ventilation in the presence of unilateral lung disease (e.g., failing transplanted lung) can lead to hyperinflation of the contralateral lung, mediastinal shift, and haemodynamic instability due to differences in airway resistance or lung compliance. In such situations, independent or differential lung ventilation with or without PEEP can be employed to avoid hyperexpansion and barotrauma to the native lung.^{53,66}

Pulmonary reimplantation response

Pulmonary reimplantation response manifests as non-cardiogenic pulmonary oedema (PCWP $<12 \text{ mmHg}$) in the transplanted lung with hypoxaemia (requiring a FiO_2 of 0.3 to maintain a $\text{PaO}_2 >60 \text{ mmHg}$) and alveolar and/or interstitial shadowing.⁶¹ It manifests in the early post-transplant period (within minutes to four days) without evidence of bacterial infection or rejection.⁶¹ Clearing of the PRR is progressive, with complete resolution between the sixth and 21st day.⁶¹ The mean duration of ventilation was seven days, ranging from one to 19 days, in a series of 24 patients.⁶¹ In contrast to adult respiratory distress syndrome, the prognosis of PRR is favourable with morbidity related to nosocomial infections and barotrauma from prolonged ventilation. Fluid balance should be critically controlled during the perioperative period as excessive fluid administration is believed to aggravate the clinical manifestations of PRR.

Ventilatory response

Physiologically, the implanted denervated lung exhibits bronchodilatation, decreased ventilatory response to hypercapnia, and decreased pulmonary clearance and cough reflex. Phillipson *et al.* demonstrated that vagal blockade in awake breathing dogs results in no change in resting carbon dioxide tension.⁶⁷ Vagal sectioning results in reduced respiratory rate and higher tidal volumes maintaining the level of ventilatory response

during exercise. Increase in ventilatory response during CO₂ rebreathing after lung transplantation is principally due to an increase in tidal volume for either single or bilateral lung transplant recipients.⁶⁸ The single lung transplant recipients, however, show an ability to increase the respiratory rate in response to CO₂ rebreathing, whereas the bilateral lung transplant recipients do not.⁶⁸ In DLT recipients, the maximal ventilation achieved during hypercapnic ventilation is less than the predicted maximal voluntary ventilation.⁶⁹ The increase in PaCO₂ secondary to opioid depression might be exacerbated in patients following DLT. Respiratory muscle weakness may also be a factor limiting ventilatory responsiveness in the face of altered pulmonary mechanics or function, i.e., restriction, obstruction, or a mixed pattern.⁶⁹ Frost *et al.* could not identify any other contributing cause for the disproportionate blunting of the hypercapnic ventilatory response to the degree of pulmonary dysfunction.⁶⁹ Comparison of the hypercapnic ventilatory responses of transplant patients with similarly obstructed or restricted control subjects would further clarify the contribution of pulmonary mechanics *vs* pulmonary denervation in the control of breathing.⁶⁹

Haemodynamic and fluid management

For haemodynamic stability, optimization of preload and afterload is essential. Development of a reimplantation response manifesting as low pressure pulmonary oedema secondary to microvascular leak is common in the early postoperative period.⁶¹ There is, however, concern regarding the amount of crystalloid that can safely be administered without adversely affecting graft function.⁶¹ According to Karanikolas *et al.* the amount of fluid administered to maintain haemodynamic stability during lung transplantation did not adversely affect the graft function (PaO₂/FiO₂) or time to extubation.⁷⁰ To augment urine output, loop diuretics are usually administered in the early postoperative period.⁶⁴

Postoperative haemorrhage is more common in patients requiring CPB during transplantation.⁶⁴ Cardiopulmonary bypass is associated with increased blood transfusion requirement, longer postoperative ventilation, and longer hospital stay in patients undergoing DLT for cystic fibrosis.⁴⁰ In another study, use of CPB was associated with considerably increased transfusion of packed erythrocytes, platelets, and cryoprecipitate.⁵⁴ However, according to Triantafyllou *et al.* use of CPB did not adversely affect the outcome expressed in terms of time to extubation, duration of ICU stay, and the time required to reach a room air PaO₂ >60 mmHg.⁶⁰ Administration of aprotinin decreases postoperative blood loss and blood product

requirement in patients requiring CPB during lung transplantation.⁷¹ Blood products should be filtered through a 40 µm filter before administration, as the absence of lymphatics in the transplanted lung increases the propensity for interstitial pulmonary oedema.³⁸ In a canine model, use of uncoated, as well as heparin coated, CPB had an adverse effect on arterial oxygenation (two hours after reperfusion), cardiac index and mean arterial blood pressure, and increased postoperative blood loss compared with the group that did not undergo CPB.⁷²

Pulmonary hypertension and transient graft dysfunction can complicate the postoperative course following lung transplantation. It has been demonstrated in a canine model that the use of CPB during lung transplantation greatly exaggerates pulmonary vasomotor dysfunction in the transplanted lung due to much greater impairment of both endothelium-dependent cyclic guanosine monophosphate and β adrenergic cyclic adenosine monophosphate-mediated relaxation. This dysfunction may contribute to considerably higher pulmonary vascular resistance in the transplanted lung.⁷³ Nitric oxide administration, 10–80 ppm, can improve oxygenation and decrease pulmonary artery pressures without adverse haemodynamic effect; however, transient methaemoglobinaemia can develop secondary to prolonged treatment.⁷⁴ Administration of prostaglandin E₁ also improves early graft function (oxygenation) in mongrel dogs following lung transplantation.⁷⁵

Pain management

Patients undergoing thoracotomy experience severe respiratory impairment postoperatively secondary to severe pain. The provision of postoperative analgesia is complicated by pulmonary denervation, wide thoracotomy incision, and residual pulmonary impairment. Epidural, compared with *iv* opioid analgesia, decreases the time to extubation and intensive care unit stay of these patients.⁷⁶ An epidural catheter can safely be placed preoperatively in these patients while the coagulation status is normal.⁷⁷ Thomas and Siegel reported excellent postoperative analgesia and earlier extubation (13-hr postoperatively) in a SLT recipient administered a bolus of epidural hydromorphone, 1.5 mg (in 10 ml preservative free saline), followed by an epidural infusion at 0.25-mg·hr⁻¹.⁷⁸ Body *et al.* reported postoperative hypercapnia associated with epidural analgesia in a series of 29 patients undergoing SLT or BSLT. These patients received an epidural infusion of bupivacaine 0.125–0.25% (mean rate: 5.2–8.3 ml·hr⁻¹) with either fentanyl 5 µg·ml⁻¹ or meperidine 2.5 mg·ml⁻¹.⁷⁹ Hypercapnia could have been due to the central action of epidural opioids, or to a failure to reset brainstem or

peripheral chemoreceptors, or due to underlying mechanisms described previously.⁶⁷⁻⁶⁹

Antimicrobials and immunosuppression

Both donor and recipients are subjected to bronchoscopy preoperatively. Antibiotic coverage, based on Gram-stain and culture results from the donor bronchial washings, has decreased the incidence and severity of bacterial infection.^{80,81} Cephalosporins are usually administered during the first 24–48 hr postoperatively and are discontinued if there are no symptoms or signs of pneumonitis or sepsis. Investigation of any unexplained fever or pulmonary infiltrates should be supplemented with bronchoscopy, bronchoalveolar lavage and protected brush specimens with quantitative cultures.^{64,81} Third or fourth generation cephalosporins are preferred to aminoglycosides to avoid aminoglycoside-related nephrotoxicity. These patients also receive trimethoprim and sulfamethoxazole for prevention of *Pneumocystis carinii*.⁸² Ganciclovir alone or in combination with CMV hyperimmune globulin is administered for prevention of CMV if either the donor or recipient has a CMV-seropositive test result before surgery.^{8,81,83} The prophylactic use of ganciclovir has reduced the prevalence of CMV infection from 71% to 16%.⁸ Commonly used maintenance immunosuppression protocols involve administration of prednisone, azathioprine and cyclosporine.⁸ Induction protocols may vary between centres as early use of corticosteroids for immunosuppression after transplantation was thought to affect airway healing adversely. Methylprednisolone, 500 mg *iv*, is usually administered just before revascularization of the implanted lung followed by a maintenance dose of 0.5–4 mg·kg⁻¹·day⁻¹ for three to four days.^{6,39} Thereafter, prednisone 0.5 mg·kg⁻¹·day⁻¹ *po*, is instituted and gradually tapered to a low maintenance dose. Alternatively, T-cell lytic therapy can be employed for induction immunosuppression. Routinely used preparations include ATGAM, a polyclonal antithymocyte globulin, and OKT-3, a Murine monoclonal antibody (antibody to T3 antigen of human T cells). Acute adverse effects of T-cell lytic therapy include fever, dyspnoea, pulmonary oedema, hyperglycaemia, hypotension, myalgia-arthralgia syndrome and malaise.^{84,85} Besides acute adverse effects, there is an increased incidence of lymphoproliferative disorders and CMV infections.^{85,86} T-cell lytic therapy is adjusted by monitoring the absolute number of peripheral T-cell subset (CD-3 T lymphocytes) by flow cytometry and by observing the adverse clinical effects of therapy.^{84,85} Cyclosporine *iv* is administered during first two to three days at an initial dose of 100–150 mg·24-hr⁻¹. Cyclosporine *iv* is tapered when therapeutic levels are achieved with oral dosing.

Trough blood concentrations are obtained one hour before the oral dose to adjust the dosing schedule to maintain a therapeutic level of 400–500 ng·ml⁻¹, based on radioimmunoassay, or 250–300 ng·ml⁻¹ using a high-pressure liquid chromatography assay.⁸⁰ Azathioprine, 1.5 mg·kg⁻¹ *iv*, is administered as a single daily dose during the first week, and thereafter it is administered *po*. White blood cell count is monitored to adjust the dose of azathioprine, with decreased dose for white blood cell count <6000·mm⁻³.⁸⁰ Effects of a new immunosuppressant drug, FK 506, have recently been compared with cyclosporine in both paediatric and adult patients.^{87,88} Results are encouraging in children and in preliminary randomized trials in adults. Use of FK 506 reduced the incidence of acute rejection and improved the intermediate graft survival at six months as compared to the cyclosporine-treated group in the adult population.⁸⁸

Cyclosporine-induced nephrotoxicity occurs in 25–75% of the recipients and is usually dose related and reversible.⁸⁹ Other drugs used during the peritransplant period such as amphotericin B, furosemide, aminoglycosides, and trimethoprim/sulfamethoxazole appear to increase the cyclosporine toxicity.⁹⁰ Cyclosporine-induced hypertension, a defect of sodium excretion, occurs in approximately 25–50% of patients.^{8,90}

Delayed complications after lung transplantation

Posttransplant patients receive immunosuppression therapy for life and are at increased risk of infection. Early recognition, differentiation of infection from rejection, and prompt initiation of therapy are of critical importance.

Infection

Bacteria are the most likely organisms to cause infection during the early posttransplantation period, whereas opportunistic pathogens such as CMV are the frequent cause of infection later as the T-cell mediated immunity wanes over weeks following immunosuppression.⁸¹ Infection usually arises within the allograft (80%) and accounts for the majority of the complications.⁸ Gram negative bacterial pneumonias are the most common postoperative infections and are associated with a lower mortality.⁸ Infectious complications with pan-resistant (resistant to most antibiotics) *Pseudomonas* species or *Pseudomonas cepacia* are associated with a higher mortality and earlier and more frequent development of obliterative bronchiolitis (OB) in survivors.³⁹ Viral and fungal (e.g., CMV, Epstein Barr Virus, *Candida*, *Cryptococcus* and *Aspergillus*) infections are associated with a higher mortality.⁸

Cytomegalovirus infection varies in severity from asymptomatic shedding of the virus to CMV syndrome

and pneumonitis. One series reported 87% and 71% prevalence of CMV infection, if either the donor or recipient was seropositive for CMV, respectively.⁸ In contrast, CMV infection develops in <10% of seronegative patients receiving lung allografts from a seronegative donor. Infection in the seronegative recipients is more likely to be symptomatic (95% *vs* 45%) and fatal (45% *vs* 10%) than in the seropositive recipients.⁸ By using multivariate analysis, Bando *et al.* demonstrated that CMV mismatch, absence of CMV prophylaxis, and development of CMV disease are severe threats for death, rejection, and infection after pulmonary transplantation.⁹¹ Prevention of CMV disease improves survival by decreasing the prevalence of infection and rejection.⁹¹

Acute rejection

Acute rejection episodes can be either asymptomatic or present with fever, shortness of breath, generalized fatigue, and hypoxaemia. Surveillance includes frequent chest-X rays, ABG analysis, pulmonary function tests (10% decrease in FVC and FEV₁ is considered significant),⁹² and transbronchial lung biopsy.⁹³ Sensitivity and specificity of the transbronchial biopsy for diagnosing acute rejection has been reported to be 84% and 100%, respectively.⁹³

Given the short and long term adverse effects of rejection, aggressive therapy following positive transbronchial biopsy is critical. Dramatic clinical response with improvement in gas exchange, spirometry, and radiographic appearance to a pulse dose of methylprednisolone, 500–1000 mg *iv*, is considered to confirm the diagnosis of acute rejection.³⁹ Treatment of acute rejection includes a three day course of high dose boluses of methylprednisolone *iv* followed by oral prednisone. OKT3 therapy can be employed for steroid resistant, high grade, or relapsing acute lung rejection during the first six months.⁸⁵

Obliterative bronchiolitis

Obliterative bronchiolitis is defined clinically by an obstructive pulmonary function defect and histologically by obliteration of the terminal bronchioles and is the main long term complication following lung transplantation. The incidence of OB has been reduced with augmented immunosuppression, and progression of the disease has also been slowed.⁹⁴ The origin of OB remains unclear, however, it is believed to be a manifestation of chronic allograft rejection.⁹⁴ Chronic rejection is defined by histologic evidence of OB in the absence of infection, and is associated with dyspnoea, cough, and a progressive restrictive and obstructive defect of the small airways.⁹⁴ Improved management of chronic rejection will require closer surveillance, earlier treat-

ment with more effective immunosuppressants, and a better understanding of basic pathophysiology of the allogenic process.

Causes of death

Infection is the most common cause of early death (<90 days posttransplant), whereas primary organ failure manifesting as diffuse alveolar damage/adult respiratory distress syndrome is the most common complication and the second most common cause of early death (Table III).^{1,39,91} Chronic rejection in the form of OB and infection (excluding CMV) are frequent causes of delayed morbidity and mortality (90 days posttransplant) following lung transplantation (Table IV).^{1,39,91}

Anaesthesia in patients with lung transplant

Lung transplant patients may require anaesthesia for follow up procedures (e.g., assessment of airway healing, transbronchial biopsy), surgical exploration for infectious complications or bleeding, retransplantation, or unrelated surgical procedures. Defects in airway healing leading to bronchial stenosis or airway dehiscence are frequent complications requiring placement of airway stents or reanastomosis. During preoperative evaluation, special emphasis is placed on function of the transplanted lung, presence or absence

TABLE 3 Causes of Early Transplant Recipient Deaths¹

Cause of death	%/n (Total)*
Infection (Other than CMV)	29%
Primary Organ Failure	13%
Cardiac Failure	9%
Haemorrhage	6%
Multi-organ Failure	6%
Airway Dehiscence	5%
Rejection	5%
CMV	5%
Other	22%

*Values are percentage of total number (n=848)

TABLE 4 Causes of Delayed Transplant Recipient Deaths¹

Cause of death	%/n (Total)*
Bronchiolitis Obliterans/Rejection	29%
Infection (Other than CMV)	24%
Malignancy	6%
CMV	5%
Respiratory Failure	5%
Haemorrhage	4%
Multi-Organ Failure	3%
Cardiac Failure	2%
Other	21%

*Values are percentage of total number (n=932)

of infection and/or rejection, and side effects and interactions of immunosuppressive therapy. In patients receiving steroids, administration of a perioperative dose of steroids is common, although controversial. Appropriate antibiotic prophylaxis is administered in the immediate preoperative period. All peripheral, central and arterial cannulae should be inserted under full aseptic techniques and intravenous infusion ports should be capped and kept sterile. Fluids should be administered judiciously as the transplanted lung is devoid of lymphatic drainage. Concerns about altered lung physiology (i.e., denervation) have been found to be of theoretical rather than practical significance.⁴⁴ Peak airway pressures should be minimized during IPPV to avoid damage to the bronchial anastomosis. High frequency jet ventilation via transbronchial catheter has been used in the management of airway complications following lung transplantation.⁹⁵

Patient survival and future directions

Survival after lung transplantation has improved progressively during the last decade. According to the St. Louis International Lung Transplant Registry data, actuarial survival following lung transplantation is 71% (one-year), 63% (two-year), 56% (three-year), 50% (four-year), 45% (five-year), 39% (six-year) and 34% (seven-year). Currently, one year survival for patients undergoing BSLT/SLT approaches 80–90% in some centres. Survival in the paediatric age group is 66% (one-year), 57% (two-year) and 48% (three-year).¹ Results are better for patients with emphysema than for those with cystic fibrosis, pulmonary hypertension, and pulmonary fibrosis (Figure 1). Patients undergoing BSLT do better than those undergoing SLT (Figure 2). This may be related to a better tolerance of chronic graft dysfunction in patients with bilateral lung replacement. Survival for patients undergoing retransplant is 49% (one-year), 42% (two-year) and 37% (three-year).¹

Pulmonary function improves markedly following lung transplantation.⁹⁶ The FEV₁, FVC and MVV (maximum ventilatory volume) are increased in all recipients except in patients with pulmonary hypertension. The PaO₂ also improves, and oxygen dependent patients are able to function without oxygen therapy.⁹⁷ Despite improvement, these patients still have severe exercise limitation following lung transplantation. Maximum work rates and VO₂ max are approximately half that of predicted and the anaerobic threshold is also reduced.⁹⁶ This persistent abnormality in exercise capacity has been attributed to chronic muscle deconditioning with accompanying abnormal cardiovascular response to exercise. Following bilater-

FIGURE 1 Five Year Actuarial Survival by Diagnosis (From the St. Louis International Lung

Transplant Registry Data); EMP (emphysema), CF (cystic fibrosis), PF (pulmonary fibrosis), PPH (primary pulmonary hypertension)

FIGURE 2 Five Year Actuarial Survival by Transplant Type (From the St. Louis International

Lung Transplant Registry Data); SLT (single-lung transplant), BSLT (bilateral single-lung transplant), DLT (En-bloc double-lung transplant).

al volume reduction surgery (excision of 20–30% of the volume of each lung) in patients with severe COPD, Cooper *et al.* reported an improvement in FEV₁ by 82% and considerable reduction in total lung volume, residual volume and trapped gas.⁹⁸ These changes have been associated with marked relief of dyspnoea and improvement in exercise tolerance and quality of life. This procedure may serve as a possible alternative to lung transplantation for a select group of patients, or may act as a bridge to transplantation at a later date when subsequent deterioration occurs.

Delayed complications of chronic rejection/OB and infection have become the most important challenges limiting the benefit of lung transplantation. The improved long term outlook will depend to a large extent on better treatment of OB and infection. Other issues including shortage of donor organs, short preservation times, and financial costs to the healthcare system remain to be fully addressed. Current areas of active research include prolongation of preservation-ischaemic times, prevention of reperfusion injury, and feasibility of pulmonary xenotransplantation.⁹⁹ Xenotransplantation holds the promise of an abundant supply of donor organs; however, considerable advances in this area will be required before this procedure becomes a reality. Average cost per lung transplantation is estimated to be US\$164,989 followed by post-transplant maintenance charges of \$11,917/mo (first-year) and \$4,525 thereafter.¹⁰⁰ Expenses incurred by patients on waiting list are estimated to be \$3,395/mo.¹⁰⁰

Summary

Lung transplantation offers hope of improved quality of life in patients with end stage lung disease. The major limitation of the procedure relates to the higher costs with marginal improvement in life expectancy compared with conservative treatment (5.89 yr *vs* 5.32 yr).¹⁰⁰ In summary, although the future of lung transplantation seems promising with potential for rapid growth, its economic impact on the healthcare system will continue to draw attention.

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