Occasional reviews

The donor lung: conservation of a precious resource

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Lung transplantation became a reality in 1963 when Dr James Hardy performed the first successful single lung transplant¹ in a patient with chronic pulmonary disease and bronchogenic carcinoma. His patient survived 18 days, eventually succumbing to renal failure. His opportunity for success was hampered by a lack of adequate immunosuppressive agents, limited perioperative monitoring, and a lack of adequate support systems such as haemodialysis. Over the next two decades numerous lung transplants were performed. Although all ended as failures, valuable information and experience accumulated in the areas of immune system alteration, diagnosis and treatment of rejection, and opportunistic infections.² The role of prophylactic antibiotic regimens was better defined. Since the mid 1980s many of these issues have been resolved, and many centres currently perform lung transplantation with progressively better survival rates. The availability of cyclosporin as an immunosuppressive agent allowed reduced doses of corticosteroids to be used and has had a dramatic impact on the successful outcome of lung transplantation. The latest report from the United Network for Organ Sharing (UNOS)³ in the USA recognises 95 centres registered to perform heart-lung transplants and 91 to perform lung transplantation. As more centres have the technological expertise to perform transplantation, and as this technology expands to treat a wider range of chronic lung diseases, there has been an inevitable increase in the number of patients listed for transplantation and, consequently, significant prolongation of waiting times. This is a problem which is now affecting all countries with active transplant programmes; in this paper these problems are discussed in relation to data for transplantation in the USA.

Transplant physicians have constantly to analyse this fluctuation in waiting times. Patients must "get in" in the UNOS list at a time when they are significantly and irreversibly impaired by their chronic pulmonary disease, yet while still healthy enough to survive the prolonged wait. Although impossible to predict, the hope is that when the transplant actually occurs, the patient still preserves a minimum of strength and physical conditioning to survive the surgery. Even when many objective parameters are used in selection of

transplant candidates, there is always a component of luck and conjecture in this process.

Most transplant centres follow general criteria for the inclusion of patients on a waiting list. Patients with chronic obstructive lung disease are usually considered for transplantation when they are functionally disabled, reaching forced expiratory volume in one second (FEV₁) of <20–25% of normal, when there is significant hypercapnia, hypoxaemia, or secondary pulmonary hypertension complicating the course of the disease, or when there is a rapid decline in functional parameters while receiving optimal medical treatment.⁴

Patients with pulmonary fibrosis have increased short term mortality when their FVC is <65% of normal and they fail to respond to corticosteroid agents. Patients with pulmonary fibrosis with a forced vital capacity (FVC) <65% of normal who have a low transfer factor (Tlco) of <30% predicted, and those becoming hypoxic with exertion have a poor prognosis⁵ and should be considered for transplantation. Patients with cystic fibrosis having an FEV₁ of <30% of predicted, with either hypoxia or hypercapnia, or having a rapid decline in lung function with recurrent exacerbations should also be included.^{4,6} Patients with severe primary pulmonary hypertension (mean PA ≥50 mm Hg) with increased central venous pressure and poor cardiac index (≤2.5) who do not respond to vasodilators are at risk for increased mortality⁷ and are usually considered for single or double lung transplantation.

Despite the careful use of all these criteria for listing patients at an appropriate time in the course of their illnesses, 15–20% of all patients listed for lung transplantation die while waiting for a suitable donor.³

Magnitude of the problem in the USA

Figure 1 shows the number of patients registered for transplantation in the USA as reported by UNOS from 1988 to December 1997. In 1988, 69 patients were registered for lung transplantation and 205 were listed for heart-lung transplantation. On 24 December 1997 there were 2678 patients registered for lung transplantation (a 17-fold increase), while the number of cases registered for heart-lung transplantation remains relatively unchanged at 236 patients (heart-lung candidates not shown in the figure).

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Figure 1 Graph showing all patients listed for single and double lung transplantation in the USA from 1988 to 1996 as reported by UNOS (solid bars), the number of patients actually transplanted (hatched bars) and the number of patients dying on the waiting list (white bars). Using the trend for each variable from 1988 to 1996, a projection is made for the number of patients listed, transplanted, and dying on the waiting list from 1997 to 2000. It is projected that in the year 2000 nearly 3500 patients will be listed, 1500 hopefully will be transplanted and, unfortunately, around 600 will die on the transplant list, assuming that the same trends will be maintained. Heart-lung transplants are not included in the figure.

This large increment in patients listed for transplantation has been accompanied by an increase in available organ donors. However, despite this increase, an ever larger number of patients cannot be transplanted in a timely basis. In 1993, 1994, 1995 and 1996 there were enough organs to transplant only 667, 723, 871 and 805 patients, respectively. The number of heart-lung transplants performed on a yearly basis since 1990 is much more limited, averaging 58 heart-lung transplants performed in the entire country (ranging from 48 in 1992 to 39 in 1996). The increasing number of patients listed, coupled with longer waiting times, has resulted in more patients dying on the waiting list. In 1988 there were 16 lung transplant candidates and 61 heart-lung transplant candidates (total 77 patients) who died while awaiting transplantation. In 1996 there were 385 patients from the lung transplant group and 48 from the heart-lung group (total 433) who died awaiting transplantation.

The figure also shows the projected number of patients listed, patients transplanted, and

those dying while listed for transplant for the year 2000 if the current trends persist over the next four years. It is likely that approximately 3500 patients will be listed, while only about 1500 may receive suitable organs to be transplanted. Over 600 patients are estimated to die awaiting transplantation.

Patients currently listed for transplantation are unevenly distributed across the USA. Figure 2 shows the 11 UNOS regions across the country with the respective number of patients listed for lung and heart-lung transplantation in each region. Regions 2 (east) and 8 (mid-west) have the largest number of patients listed while regions 6 (north west) and 3 (south east) are those with the shortest waiting lists.

The disproportion between patients listed compared with those transplanted has resulted in progressively longer waiting times for those hoping to receive a lung transplant. The median waiting time for patients listed in 1988 was 386 days. This declined to the shortest waiting time by 1990 (228 days) but then progressively increased to 553 days in 1994. The waiting time for lung transplantation today equals the usual waiting time for patients listed for heart-lung transplantation. It is not unusual for lung transplant candidates to face waiting times around 1.5–2 years. The extreme limitation of lung donors does not allow room to create any special status for patients who suffer an acute deterioration while listed for transplantation.

These statistics have an obvious conclusion; currently, the main limiting factor to lung and heart-lung transplantation is the restricted availability of donors. The trends over the last five years suggest that it is unlikely that a significant change in patterns of organ donation will occur and that the shortage of available donors will continue to worsen.

These facts will produce two inevitable consequences: (1) increasingly longer waiting times and increased difficulties deciding the best time to include a patient in the waiting list; (2) a larger number of patients dying while awaiting transplantation. This situation imposes increased responsibility on transplant physicians and centres to assure efficient use of available lung donors. There is also a compelling need to shift some of the patients listed for transplantation to other therapeutic avenues.

Figure 3 shows the distribution of lung transplants according to diagnosis as reported by the St Louis International Lung Transplant Registry. The data reported include an accumulated 5280 lung transplants reported to the Registry up to 1996. The largest number of transplants have been performed in patients with chronic obstructive lung disease. Around 40% of all lung transplants were performed to treat either smoking induced COPD or α_1 -antitrypsin deficiency related emphysema, followed by pulmonary fibrosis, cystic fibrosis, primary pulmonary hypertension, Eisenmenger's complex, bronchiectasis and others; 139 of these procedures were re-transplants.

Figure 2 Division of the USA into the 11 UNOS regions with the number of lung transplant candidates listed per region. Numbers in parentheses reflect the numbers of patients listed for heart-lung transplantation in each region on 30 June 1997.

Figure 3 Distribution of 5280 lung transplants performed up to 1996 as reported to the St Louis International Lung Transplant Registry. Chronic obstructive pulmonary disease and patients with emphysema secondary to α_1 -antitrypsin deficiency account for 2029 transplants or 38.4% of the total.

Strategies to overcome limitations to lung transplantation

Potential strategies to overcome the limited number of organ donors are necessary. These strategies can be categorised into the following groups:

- (1) Maximise the use of available organs:
 - (a) expand the indications for single lung transplants, while restricting the use of double lung and heart-lung transplantation only when absolutely necessary;
 - (b) explore further the use of marginal donors;
 - (c) use of living related donors in specific circumstances.
- (2) Explore the use of medical/surgical alternatives for conditions currently managed with lung transplantation:
 - (a) lung volume reduction surgery for emphysema;
 - (b) use of chronic prostacyclin infusion for primary pulmonary hypertension.
- (3) Critical review of the use of donated lungs for indications with poor prognosis:
 - (a) re-transplantation;
 - (b) lung transplantation in the elderly.
- (4) Other alternatives to organ donation: xenotransplantation

MAXIMISING USE OF AVAILABLE DONORS

Expanding indications for single lung transplants while restricting use of double lung and heart-lung transplantation to only when absolutely necessary

In 1981 the first successful heart-lung transplant (HLT) associated with long term survival was reported by the transplant group at Stanford University.⁸ The technique was initially used to treat patients with terminal primary pulmonary hypertension (PPH) and others with Eisenmenger's complex. In 1983 the Toronto Lung Transplant Group reported the first long term survivor provided with a single lung transplantation (SLT) to treat terminal idiopathic pulmonary fibrosis.⁹ By 1990 HLT was used not only to treat patients

with PPH, Eisenmenger's complex, and other cyanotic congenital heart diseases associated with pulmonary hypertension, but also pulmonary diseases such as cystic fibrosis, emphysema and other chronic conditions.¹⁰ Heart-lung transplant recipients with cystic fibrosis became heart donors themselves at the time their organs were removed in what used to be called the "domino" technique.

As the technology of double lung transplantation (DLT) and SLT evolved, their indications have expanded. Survival and function of DLT improved significantly when the original "en bloc" technique using a tracheal anastomosis¹¹ was modified using sequential bi-bronchial anastomosis.¹² When availability of donors became an obvious limiting factor to performing HLT and DLT, more clinical experimentation was done with SLT.¹³⁻¹⁵ By limiting HLT to cases of Eisenmenger's complex and other cyanotic congenital diseases, and using SLT whenever possible, three recipients (two single lungs, one heart) can potentially benefit from each donor.

Single lung transplantation was initially used mostly to treat natives with idiopathic pulmonary fibrosis with acceptable survival rates and good functional outcomes. For a long time it was believed that SLT should not be performed in patients with COPD.¹⁶ It was assumed that a single lung with normal compliance and resistance in a patient with a contralateral native emphysematous lung would suffer from ventilation and perfusion mismatch. Despite theoretical concerns, once single lung transplantation was performed in patients with COPD,¹⁷ it was found that this technique was not only successful but that COPD recipients of single lung transplants had the best prognosis for long term survival.¹⁸ Pulmonary function increases more after DLT than SLT in patients with COPD, but exercise capacity is similar, as is long term survival. Similarly, SLT was utilised for the management of patients with PPH. Although the intraoperative and postoperative management of patients with PPH subjected to SLT is challenging, the long term outcome is satisfactory and comparable to other indications for SLT.¹⁹ Survival rates for patients with PPH subjected to SLT are similar to DLT and superior to HLT.

Currently, most centres reserve double lung transplantation for conditions characterised by septic bilateral lung disease such as cystic fibrosis and bilateral bronchiectasis. Single lung transplantation is an acceptable alternative for chronic obstructive lung disease, interstitial lung disease, primary pulmonary hypertension, and selected cases of Eisenmenger's complex due to persistent atrial septal defect where a surgical repair of the defect is associated with a single lung transplant.

The judicious use of HLT and DLT, reserving these techniques only for patients who cannot be helped by SLT, maximises the limited pool of donors for the largest number of patients.

Exploring further the use of marginal donors

Organ donation in the USA comes from pure voluntary and altruistic motives where families of patients with an established diagnosis of brain death are approached for possible organ donation. Generally accepted criteria for adequate lung donors include patients younger than 55 years, without history of pulmonary diseases, without significant chest trauma, with accumulated smoking history of <20–30 pack years, evidence of a chest radiograph clear of infiltrates, requiring peak pressures on the ventilator of <30 cm H₂O, with a Pao₂/Fio₂ of ≥300 and without evidence of gross purulent secretions in a bronchoscopic procedure.²⁰ Donors must be screened for septicaemia, active tuberculosis, HIV, viral hepatitis, viral encephalitis, Guillian-Barre syndrome, current intravenous drug abuse, and malignancy.

As the experience of managing immediate complications following transplantation improves, the criteria for choosing donors can be expanded. A study by Sundaresan and coworkers reviewed the outcome of transplant patients using marginal donors selected from patients who had infiltrates in chest radiographs, evidence of chest trauma (contusion or pneumothorax), accepting donors older than 55 years, smoking history >20 pack years, and accepting Pao₂/Fio₂ ratio <300 mm Hg.²¹ The postoperative outcomes of recipients of these marginal organs were not different from those recipients of organs from patients meeting the classical criteria for organ donation. Specifically, there were no differences in survival, time of extubation, or postoperative alveolar–arterial oxygen gradients.

In many circumstances a single lung could be used from donors with marginal gas exchange who have a unilateral infiltrate with a clear contralateral lung. In these circumstances an experienced transplant physician can decide to use the non-involved lung aided by a bronchoscopic evaluation of the donor if the procedure shows the lung to be used to be free of significant purulent tracheobronchitis.

A potential donor subjected to prolonged intubation and mechanical ventilation alone should not be a contraindication to lung transplantation. An electively intubated donor, who evolves to a status of brain death, who has good gas exchange, a clear chest radiograph and has acceptable bronchoscopic findings can be used as a donor after 5–7 days of mechanical ventilation as shown in a study by the Cambridge group. These considerations by surgical teams potentially expand the limited pool of lung donors.

Use of living related donors in specific circumstances

In 1990 the first living related donor lung transplant (LRDT) was reported by the Stanford transplant group.²² Up to June 1996 the UNOS transplantation information site reported a total of 78 LRDTs. The current status of this new approach to transplantation is based on harvesting lower lobes from healthy donors (usually parents or relatives of a child or very young adult) to perform bilateral lobar

transplantation to patients with cystic fibrosis. Early reports of this technique on 36 recipients of lobar transplants from living related donors showed a one year survival rate of 70%, with good lung function.²³ Episodes of acute rejection and bronchiolitis obliterans have been reported among these recipients with a lower incidence than among cadaveric transplants. So far there has been no mortality reported among donors, who have shown an 18% mean decrease in vital capacity. This approach to lung transplantation offers a potentially life saving procedure to young patients with cystic fibrosis or similar conditions, without the uncertainties of the prolonged waiting time that occurs with cadaveric organ donors.

Transplant centres using this technique face significant challenges. The surgery involves the use of three surgical teams working simultaneously. The implantation involves development of anastomotic techniques in airways and vessels of limited size and length, making the procedure technically challenging. Besides the purely technical difficulties presented by LRDLT there are multiple ethical and psychological dilemmas surrounding preparation and selection of donors that still do not have clear definition. Despite these drawbacks, LRDLT offers an alternative to cadaveric organ transplantation. As more centres gain experience with this approach, a well selected population of young patients with end stage lung disease will probably benefit in the future from further developments.

EXPLORING THE USE OF MEDICAL/SURGICAL ALTERNATIVES FOR CONDITIONS CURRENTLY MANAGED WITH LUNG TRANSPLANTATION

Lung volume reduction surgery for emphysema

The reintroduction of lung volume reduction surgery to improve end stage emphysema in 1995 by Cooper and associates²⁴ has been followed by multiple clinical studies using surgical techniques such as sternotomy, thoracoscopic lung resection, and the use of laser therapy with the objective of effectively reducing excessive hyperinflation of emphysematous lungs to improve lung function.

A recent review of the current status of lung volume reduction surgery for emphysema summarised 16 clinical studies involving a total of 1331 patients undergoing volume reduction²⁵ using laser (four groups), combined laser and resection (two groups), resective thoracoscopy (five groups), and open sternotomy (five groups). The mean preoperative FEV₁ ranged from 19% to 30% of normal, with mean residual volumes (RV) from 197% to 290% of predicted, and mean six minute walking tests between 589 and 1175 feet. These groups reported mortality rates ranging from 0% to 18%. The increase in FEV₁ varied from 13% to 97%, the decrease in RV from 11% to 33%, and the increment in the distance in the six minute walking test from 14% to 104% over baseline values. Most of these groups reported only short term follow up (3–6 months), although a few groups now have data available one or two years after surgery. The severity of obstructive lung disease included in these

Table 1 Comparison of lung function following volume reduction surgery, single lung transplantation and double lung transplantation in patients with COPD

	Preoperative FEV_1	Change in FEV_1 at 6 months	Change in FEV_1 at one year	Total mortality
Volume reduction	0.72 (0.26)	79% increase	83% increase	3% (1/33)
Single lung transplant	0.48 (0.12)	231% increase	212% increase	10.2% (4/39)
Double lung transplant	0.49 (0.13)	498% increase	518% increase	16% (4/25)

FEV_1 = forced expiratory volume in one second.

Taken from Cooper *et al.*²⁶

studies is similar to that found in patients listed for lung transplantation.

Cooper and collaborators reported a comparison of early functional results after volume reduction or lung transplantation in patients with chronic obstructive pulmonary disease.²⁶ Their data are summarised in table 1.

They showed significant improvement in FVC, six minute walking tests, and gas exchange in all the groups. Although the magnitude of improvement was superior among transplanted patients, particularly for recipients of double lung transplants, improvement was similar to lung volume reduction surgery. They concluded that, in well selected patients, volume reduction surgery is a useful alternative to lung transplantation. In addition, volume reduction avoids the complications of combined immunosuppressive therapy, as well as the larger morbidity and mortality associated with transplantation. Our group has recently reported changes in lung function and gas exchange comparing unilateral thoracoscopic lung volume reduction surgery (TLVRS) with SLT in two groups of 10 patients with a similar degree of advanced emphysema.²⁷ Follow up is reported at three months and one year after surgery. The most relevant data of this study are shown in fig 4.

As shown in fig 4, patients who underwent TLVRS had a larger increment in FVC while FEV_1 increased significantly more in SLT patients. For the group undergoing TLVRS the mean changes in FVC were 55 (17)% preop-

eratively, 67 (16)% at three months, and 72 (15)% of predicted one year after surgery compared with 46 (11)%, 52 (12)%, and 60 (9)%, respectively, for patients subjected to single lung transplantation. Although both groups showed a significant postoperative increase in FVC, the changes were larger in the TLVRS group. However, the increase in FEV_1 was significantly better for patients undergoing lung transplantation than in those who underwent TLVRS. For those undergoing TLVRS the FEV_1 changed from a mean of 23% of predicted to 29% three months later and 27% a year later, while those patients undergoing transplantation increased their mean FEV_1 from 20% of predicted preoperatively to 43% at three months and 47% at one year.

The increased FVC and FEV_1 achieved in the TLVRS group was related to significant volume reduction evidenced by the reduction of the preoperative residual volume from a mean of 273 (80)% of predicted to 190 (41)% three months after surgery, remaining at 197 (38)% of predicted a year later. Both groups had significant improvement in gas exchange. The mean preoperative $Paco_2$ and Pao_2 were 41 (7) and 60 (10) mm Hg among SLT patients; one year later the mean values were 35 and 80 (14) mm Hg, respectively. In the TLVRS group the baseline blood gases showed a mean $Paco_2$ of 43 (8) mm Hg and Pao_2 of 56 (9) mm Hg. One year after thoracoscopic lung volume reduction the mean $Paco_2$ was 35 (7) mm Hg and the mean Pao_2 was 74 (13) mm Hg. None of the transplanted patients required oxygen therapy a year after surgery while eight of 10 patients subjected to volume reduction were free of oxygen.

In this study transplanted patients required longer stays in hospital; four SLT patients had significant complications, including one with anastomotic dehiscence requiring surgical repair, one patient developed postoperative status epilepticus secondary to cyclosporin neurotoxicity, one patient was treated for recurrent acute rejection, and a fourth patient required a stent insertion due to a stenotic anastomosis. Two patients in the TLVRS group developed complications; one developed pneumothorax after removal of a chest tube and required reinsertion of the tube, and a second case had a prolonged air leak requiring a second thoracoscopy to repair the operative area. In this one year study, unilateral lung volume reduction surgery produced significant objective and subjective improvement in patients with airflow obstruction comparable to those treated with SLT. The magnitude of improvement in FEV_1 was much larger among transplanted patients; overall functional and subjective improvement was comparable with less morbidity, and without the complications of immunosuppressive therapy. Currently, the St Louis International Lung Transplant Registry reports survival rates of 77%, 69%, 62%, 53%, and 45% for the first five years on patients transplanted for COPD. Although one year survival rates appear better among volume reduction candidates, long term studies are required to evaluate survival rates of patients

Figure 4 Changes in forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) in two groups of patients with severe emphysema. Ten of these patients were subjected to unilateral thoracoscopic lung volume reduction surgery (TLVRS) and 10 patients received a single lung transplant (SLT). The left side of the figure shows preoperative FVC and FEV_1 as percentage of normal predicted and changes at three months and one year after TLVRS; the right side of the figure shows changes in FVC and FEV_1 before single lung transplantation and at three months and one year after surgery.

subjected to this type of surgery. If studies with longer follow up times show that volume reduction surgery can produce reasonably long periods of improvement, then well selected groups of patients with emphysema could receive lung volume reduction surgery instead of transplantation which would spare a significant number of organs to be used among younger candidates who have no other alternative such as those with cystic fibrosis or idiopathic pulmonary fibrosis. An NIH sponsored National Emphysema Therapy trial (NETT) is being organised to define the role of LVRS. This clinical trial is structured to study over 5000 patients in 18 centres across the USA, randomising patients with severe emphysema to either best medical therapy and pulmonary rehabilitation or LVRS; the latter group is further subdivided into two groups (bilateral lung volume reduction via sternotomy or thoracoscopy). This trial should assess the efficacy of LVRS and demonstrate whether long term survival and functional capacity of patients with emphysema does indeed improve compared with best medical therapy. It should also show if there is any advantage to the use of sternotomy compared with thoracoscopic techniques, and should give a clear idea about the duration of the functional changes induced by surgery. Indirectly, this trial may define the role of LVRS as an alternative to lung transplantation.

Use of chronic prostacyclin infusion for PPH

The latest data from the St Louis International Lung Transplant Registry reports 389 patients transplanted for PPH with survival rates of 62%, 49%, and 42% at one, three and five years, respectively. The outcome of medical therapy in patients with severe PPH has been disappointing, with only a few patients found to be responsive to chronic long term anticoagulation and high doses of calcium channel antagonists.²⁸ Over the last few years, however, several clinical studies have shown improved survival, better quality of life, and increased exercise capacity by using a long term continuous intravenous infusion of prostacyclin. This substance is a metabolite of arachidonic acid in the vascular endothelium, found to be a potent endogenous vasodilator and platelet anti-aggregating agent. Higenbottam and collaborators²⁹ showed improved one year survival rates in 44 patients with severe PPH compared with historical controls. Furthermore, when the effects of prostacyclin and heart-lung transplantation were compared, they showed a reduction in monthly mortality risk of 66% among patients treated with prostacyclin whereas transplantation reduced the risk by 18%. Barst and coworkers³⁰ reported survival rates of 87%, 72%, and 63% at one, two and three years in a group of 18 patients with severe PPH treated with long term continuous intravenous prostacyclin compared with survival rates of 77%, 52%, and 41% in controls, concluding that continuous intravenous prostacyclin resulted in sustained clinical and haemodynamic improvement and improved survival in patients with severe PPH.

Most recently, Barst and collaborators reported results of a 12 week prospective, randomised, multicentre open trial comparing the effects of a continuous intravenous infusion of prostacyclin plus conventional therapy with the use of conventional therapy alone in 81 patients with severe PPH (New York Heart Association functional class III or IV).³¹ This trial showed that prostacyclin produced symptomatic and haemodynamic improvement, as well as improved exercise endurance, quality of life, and survival in these patients. Prostacyclin therapy has its own complications, mostly related to the required use of a permanent intravenous catheter with the possible development of catheter-related sepsis and thrombosis. Also, severe complications may occur related to mechanical malfunction of the drug delivery system (pump malfunction). Side effects include headache, flushing, jaw pain, loose stools, and photosensitivity. Despite all these problems, many patients experience significant functional improvement and no longer wish to consider transplantation as a treatment option once they become used to the prostacyclin. The cost of this therapy is considerable, and in the long run could become as costly as transplantation.

Today, more than 800 patients are currently on a continuous infusion of prostacyclin for severe PPH in the United States. These recent developments, coupled with the still significant mortality associated with transplantation in severe PPH, argues in favour of considering patients diagnosed with severe PPH refractory to calcium channel antagonists to receive a continuous intravenous infusion of prostacyclin. In patients showing a favourable response to prostacyclin infusion, without evidence of right heart failure, transplantation is not necessarily indicated. Patients developing signs of right heart failure despite aggressive medical therapy may be selected for transplantation as a last resort. This approach is reasonable while new strategies for treatment are developed, such as inhaled nitric oxide,³² aerosolised prostacyclin, and aerosolised iloprost,³³ all of which are currently under investigation.

CRITICAL REVIEW OF THE USE OF DONATED LUNGS FOR INDICATIONS WITH POOR PROGNOSIS

Re-transplantation

Repeat lung transplantation has been performed in a relatively small percentage of patients.³⁴ Five types of re-transplantation have been described: (1) redo ipsilateral single lung transplantation, (2) redo contralateral single lung transplantation, (3) single lung redo after double or heart-lung transplantations, (4) redo double lung transplantation, and (5) double lung re-transplantation after a first time single lung transplant. The most common indication for re-transplantation has been obliterative bronchiolitis. The latest data reporting survival rates among re-transplanted patients with bronchiolitis obliterans from North American and European transplant centres show a 45% one year survival rate and a 35% survival rate at three years compared with overall survival rates of 72% and 56% at one and three years for

recipients of lung transplantation.³⁵ Ambulatory status prior to re-transplantation is the best predictor of survival among these patients. Most patients considered for re-transplantation have obvious deterioration in respiratory capacity and functional decline which becomes the indication for the procedure. Most of them suffer the chronic effects of immunosuppression, many have received recurrent boluses of high dose corticosteroids in efforts to reverse graft failure and chronic rejection, many have renal dysfunction from use of cyclosporin and other nephrotoxic drugs, and others have been debilitated by opportunistic infections.

The critical donor shortage, the considerable percentage of patients dying on the waiting list, and the poor outcome of re-transplantation raises considerable ethical concern regarding this alternative. The question is no longer whether re-transplantation can be done, but whether it should be done.

The most compelling reason to perform re-transplantation is derived from the close relationship usually established between transplant patients, their families, and members of the transplant team. When these patients decline progressively it becomes difficult for them, as well as for members of the transplant team caring for them, to accept the fact that few alternatives remain to alter the course of the disease.

If lung re-transplantation is to be performed at all, it should be reserved only for extremely well selected patients who remain functional and ambulatory after transplantation and who will otherwise meet the same selection criteria used for patients to undergo transplantation for the first time.

Lung transplantation in the elderly

Originally, most lung transplant centres did not perform procedures on patients older than 60 years. With the advances in technique and medical therapy that have taken place, the age limits for transplantation were extended in selected patients aged 60–65 years. In 1989 there was one patient registered for lung transplantation who was older than 65 years. From that time to 1994 a total of 63 additional patients older than 65 have been registered on the lung waiting list (UNOS Update May/June 1996). Likewise, heart-lung transplants used to be limited to patients younger than 50 years.

Figure 5 Survival rates at one, two and three years after lung transplantation as reported to the St Louis International Transplant Registry. Survival rates are shown for the total number of patients reported ($n = 5004$), for patients older than 60 years at the time of transplantation ($n = 292$), and for those undergoing re-transplantation ($n = 129$). Survival rates are lower for elderly patients and lowest for re-transplants.

This concept has changed, and from 1988 to 1994 78 patients older than 50 years have been registered for heart-lung transplants.

Figure 5 summarises data derived from the St Louis International Lung Transplant Registry, reporting yearly actuarial survival for all transplants reported to the registry ($n = 5004$) compared with yearly survival in recipients aged >60 ($n = 292$) and those undergoing re-transplantation ($n = 129$). Survival rates for patients older than 65 years have been lower than younger patients.³⁶

Lung transplantation in elderly patients is not only possible, but in a few selected cases can provide full rehabilitation in otherwise terminally ill subjects. It can be argued that, as the experience with these procedures increases, a decline in the higher morbidity and mortality associated with these subsets of lung transplantation should be expected. The same argument can be made, however, for first time transplants. The one year survival rates for lung transplants in 1988 and 1989 were 42% and 58%, respectively, while the one year survival rates for patients first transplanted in 1993 and 1994 were 76% and 74%, respectively (UNOS update, July/August 1996). Given the increasingly difficult problem of limited availability of suitable thoracic organ donors, ethical questions can be raised concerning the appropriateness of performing lung transplantation on patients who will not have the same survival rates as carefully selected young recipients of a first transplant. The answer to this question will probably raise controversial and opposite opinions. Policy decisions about these issues will need to be made in the near future, hopefully guided by consensus statements made by responsible transplant-related medical associations, or by organisations like UNOS. The shortage of organ donors will make it imperative to reassess currently accepted criteria to list patients for lung and heart-lung transplantation.

OTHER ALTERNATIVES TO ORGAN DONATION: XENOTRANSPLANTATION

High hopes are placed on the research surrounding the use of organs and tissues from animals to man (xenotransplantation). Historically, few attempts have been made using xenotransplantation. Reemtsma³⁷ transplanted chimpanzee kidneys into terminally uraemic patients and one patient survived nine months after transplantation. Starzl and coworkers attempted to transplant baboon hearts into humans without good results. His group also attempted to transplant baboon livers into patients with severe hepatic failure.³⁸

Xenotransplantation is likely to be a reality in the next decade. Currently, the main problems revolve around mechanisms to avoid rejection. When organ transplantation is attempted between two largely different species the process is called discordant xenografting. Discordant xenotransplantation produces a severe hyperacute humoral rejection, the organ undergoes hyperacute rejection with obliteration of small arteries with granulocytes, thrombocytes, and erythrocytes. This significant

rejection process is related to activation of the complement system via the classical and alternative pathways. Histopathological evidence of vascular endothelial damage and concomitant local or systemic coagulopathy will be present. If the complement trigger of humoral rejection can be avoided, then cellular rejection could be managed with conventional T cell directed immunosuppression as it is done with allografts. The best hopes rest in the research using transgenic animals, placing human complement regulating genes into the organs of pigs.³⁹ Future research may realistically produce organs from pigs which cannot be attacked by the human complement system or by human natural antibodies. Once this hurdle is cleared, further research will be needed to investigate and avoid the possibility of transmission of infectious agents from animals to humans. Multiple legal, ethical, and religious aspects will also need extensive review before xenotransplantation becomes a viable reality.⁴⁰ Despite these problems, xenotransplantation may be the only alternative left in the future (other than the creation of artificial organs) for the ever increasing population of transplant candidates.

- 1 Hardy JD, Webb WR, Dalton ML, *et al.* Homotransplantation in man. *JAMA* 1963;186:1065-74.
- 2 Bruce AR. The history of heart and heart-lung transplantation. In: Baumgartner W, Reitz B, Achuff S, eds. *Heart and heart-lung transplantation*. Philadelphia: WB Saunders, 1990.
- 3 UNOS Scientific Registry Data as of 20 September 1997 (<http://www.unos.org>).
- 4 Trulock EP. Lung transplantation. State of the art. *Am J Respir Crit Care Med* 1997;155:789-818.
- 5 Stack BH, Choo-Kang YF, Heard BE. The prognosis of cryptogenic fibrosing alveolitis. *Thorax* 1972;27:535-42.
- 6 Yankaskas J, Mallory G, and Consensus Committee. Lung transplantation in cystic fibrosis. Consensus Conference Statement. *Chest* 1998;113:217-26.
- 7 D'Alonso GE, Barst SM, Ayres EH, *et al.* Survival in patients with primary pulmonary hypertension: results from a national prospective registry. *Ann Intern Med* 1991;115:343-9.
- 8 Reitz BA, Wallwork JL, Hunt SA, *et al.* Heart-lung transplantation. Successful therapy for patients with pulmonary vascular disease. *N Engl J Med* 1982;306:557-64.
- 9 Toronto Lung Transplant Group. Unilateral lung transplantation for pulmonary fibrosis. *N Engl J Med* 1986;314:1140-5.
- 10 Bonser RS, Jamieson SW. Heart-lung transplantation. *Clin Chest Med* 1990;11:235-46.
- 11 Patterson GA, Cooper JD, Goldman B, *et al.* Technique of successful clinical double lung transplantation. *Ann Thorac Surg* 1988;44:626.
- 12 Patterson GA. Double lung transplantation. *Clin Chest Med* 1990;11:227-33.
- 13 Grossman RF, Frost A, Zamel N, *et al.* Results of single lung transplantation for bilateral pulmonary fibrosis. *N Engl J Med* 1990;322:727-33.
- 14 Levin SM, Anzueto A, Peters J. Medium term functional results of single lung transplantation for endstage obstructive lung disease. *Am J Respir Crit Care Med* 1994;150:398-42.
- 15 Pasque M, Trulock EP, Kaiser LR, *et al.* Single lung transplantation for pulmonary hypertension. *Circulation* 1991;84:2275-79.
- 16 Egan TM, Cooper JD. Surgical aspects of single lung transplantation. *Clin Chest Med* 1990;11:195-203.
- 17 Mal H, Andreassin B, Fabrice P, *et al.* Unilateral lung transplantation in end-stage pulmonary emphysema. *Am Rev Respir Dis* 1989;140:797-802.
- 18 Trevor JW, Snell GI. Early and long-term functional outcomes in unilateral, bilateral, and living related transplant recipients. *Clin Chest Med* 1997;18:245-55.
- 19 Bando K, Armitage I, Paradis R, *et al.* Indications for and results of single, bilateral and heart-lung transplantation for pulmonary hypertension. *J Thorac Cardiovasc Surg* 1994;108:1056-65.
- 20 Frost AE. Donor criteria and evaluation. *Clin Chest Med* 1997;18:231-7.
- 21 Sundaresan S, Semenkovich J, Ochoa L, *et al.* Successful outcome of lung transplantation is not compromised by the use of marginal donors. *J Thorac Cardiovasc Surg* 1995;109:1075-80.
- 22 Goldsmith MF. Mother to child: first living donor lung transplant. *JAMA* 1990;264:2724.
- 23 Starnes VA, Barr ML, Schenkel MV, *et al.* Cardiopulmonary physiology in adult and pediatric bilateral lobar transplantation recipients: one year follow-up. *J Heart Lung Transplant* 1996;15:S39 (abstract).
- 24 Cooper J, Trulock EP, Triantafyllou A, *et al.* Bilateral pneumectomy (volume reduction) for chronic obstructive pulmonary disease. *J Thorac Cardiovasc Surg* 1995;109:106-19.
- 25 Naunheim KS, Ferguson MK. The current status of lung volume reduction operation for emphysema. *Ann Thorac Surg* 1996;62:601-12.
- 26 Gaissert, Trulock EP, Cooper J, *et al.* Comparison of early functional results after volume reduction or lung transplantation for chronic obstructive pulmonary disease. *J Thorac Cardiovasc Surg* 1996;111:296-307.
- 27 Keller CA, Naunheim KS, Osterloh J. Hemodynamics and gas exchange following single lung transplant and unilateral thoracoscopic lung reduction. *J Heart Lung Transplant* 1997;16:199-208.
- 28 Rich S. Medical treatment of primary pulmonary hypertension: a bridge to transplantation? *Am J Cardiol* 1995;75:63A-66A.
- 29 Higgenbottom TW, Spiegelhalter D, Scott JP, *et al.* Prostacyclin (epoprostenol) and heart-lung transplantation as treatments for severe pulmonary hypertension. *Br Heart J* 1993;70:366-70.
- 30 Barst RJ, Rubin LJ, McGoon MD, *et al.* Survival in primary pulmonary hypertension with long-term continuous intravenous prostacyclin. *Ann Intern Med* 1994;121:409-15.
- 31 Barst RJ, Rubin LJ, Long WA, *et al.* A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. *N Engl J Med* 1996;334:296-301.
- 32 Snell GI, Salamonsen RF, Bergin P, *et al.* Inhaled nitric oxide used as a bridge to heart-lung transplantation in a patient with end-stage pulmonary hypertension. *Am J Respir Crit Care Med* 1995;151:1263-6.
- 33 Olachewski H, Walmsworth D, Schermuly A, *et al.* Aerosolised prostacyclin and iloprost in severe pulmonary hypertension. *Ann Intern Med* 1996;124:820-4.
- 34 Novick RJ, Kaye MP, Patterson A, *et al.* Redo lung transplantation: a North American-European experience. *J Heart Lung Transplant* 1993;12:5-16.
- 35 Novick RJ, Shafers HJ, Stitt L, *et al.* Seventy-two retransplants for obliterative bronchiolitis: predictors of survival. *Ann Thorac Surg* 1995;60:111-6.
- 36 Hosenpud JD, Novick RJ, Bennett LE, *et al.* The Registry of the International Society for Heart-Lung Transplantation. *J Heart Lung Transplant* 1995;14:805-15.
- 37 Reemtsma K. Xenotransplantation-a brief history of clinical experiences, 1900-1965. In: Cooper DKC, Kemp E, Reemtsma K, *et al.* eds. *Xenotransplantation. The transplantation of organs and tissues between species*. Berlin: Springer Verlag, 1991: 9-22.
- 38 Starzl TE, Fung J, Tzakis A, *et al.* Baboon-to-human liver transplantation. *Lancet* 1993;i:65-71.
- 39 Kemp E. Xenotransplantation. *J Intern Med* 1996;239:287-97.
- 40 Manzetti JD, Ankeny R, Miller D. Psychosocial and ethical issues in surgical approaches to end stage lung disease. *Clin Chest Med* 1997;18:383-90.