Editorial

The current state of lung transplantation

Early attempts at lung transplantation were uniformly unsuccessful.[1] Many recipients were having assisted ventilation before transplantation and had sepsis with multi-organ failure. The use of high dose corticosteroids as the principal method of providing early immunosuppression severely affected bronchial healing and frequently led to systemic infection.

Acute rejection was difficult to diagnose and often refractory to treatment when recognised. Dehiscence of the airway anastomosis,[1] related to bronchial ischaemia, was almost invariable in short term survivors and seemed an insuperable problem. The technical difficulties have been largely overcome by approaches that have solved the problem of bronchial healing. Immunosuppression with cyclosporin A allows more selective use of corticosteroids in the early postoperative course. Finally, the importance of selection of patients is now recognised and indications for each of the available procedures are being established.

Heart-lung transplantation

Heart-lung transplantation was introduced for the treatment for pulmonary vascular disease,[2] and has become a therapeutic option for a wide range of patients, including those with end stage lung disease.[3] Most recipients still have pulmonary vascular disease,[4] but the proportion with primary lung disease is increasing and now comprises 40% of all cases, according to the current International Registry.[5] Heart-lung transplantation was the first form of lung transplantation to be introduced successfully into clinical practice. A tracheal anastomosis heals much more reliably than a bronchial anastomosis because of the presence of coronary to bronchial collaterals.[6] More importantly, it has the advantage that all the diseased pulmonary tissue is removed. The most common pulmonary indications for heart-lung transplantation are emphysema (especially α_1 antitrypsin deficiency), bronchiectasis and cystic fibrosis. Patients with cystic fibrosis represent a large group of potential recipients and initial results of heart-lung transplantation in this group are encouraging.[7]

Successful heart-lung transplantation depends on rigorous selection of suitable candidates and, though

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individual transplant units inevitably have their own criteria, a broad consensus is emerging. The shortage of suitable donors is reflected in the upper age limit of 49 years, and all patients should have respiratory failure unresponsive to conventional medical treatment and a poor quality of life. There should be no appreciable dysfunction of other major organs, particularly the kidneys and liver. This is particularly relevant to patients with cystic fibrosis, who often have liver disease.[8] A previous sternotomy or thoracotomy is not an absolute contraindication but will increase the risk of severe postoperative bleeding from the chest wall.[9] Extensive pleural thickening visible on the chest radiograph constitutes a similar disadvantage. A pleurectomy carried out for recurrent pneumothoraces substantially increases the risk of transplantation and is a contraindication in most centres.

The current demand for heart-lung transplantation is high and about 200 potential recipients die annually of pulmonary disease in the United Kingdom.[3] The shortfall in suitable donor organs means that heart-lung transplantation cannot be offered on an emergency basis or to moribund patients; in general, patients requiring full time assisted ventilation are not considered suitable.

The overall one year survival worldwide is 60%,[5] though individual centres report survival rates as high as 71% and 78%.[10] The higher figures may reflect the use of transbronchial biopsy to diagnose rejection and strategies to protect against common opportunist organisms. Survival rates in patients with primary lung disease now appear to be similar to those in patients with pulmonary vascular disease.

Rehabilitation in survivors is excellent, with restoration of a normal life style in most and little or no functional restriction. The pattern of breathing at rest, both in the waking state and during sleep, seems to be no different from that of normal individuals.[11] Ventilation during exercise follows the pattern seen after heart transplantation, with a higher minute ventilation and tidal volume for a given oxygen consumption than in normal individuals.[12]

Though recurrence of disease in transplanted lungs remains a concern, there is so far no published evidence to suggest that this has caused clinical problems. Granulomas, however, have been seen in transbronchial lung biopsy specimens in patients undergoing transplantation for sarcoidosis (J Scott, T

Higenbottam, personal communication); but the characteristic abnormality of the respiratory mucosa in cystic fibrosis (a high bioelectrical mucosal potential difference[13]) has not been seen up to two years after heart-lung transplantation.[14] Patients with α_1 antitrypsin deficiency will be potential candidates for replacement treatment when this is available, though stopping smoking is probably more important.

Single lung transplantation

Single lung transplantation offers an alternative approach for patients with chronic fibrotic pulmonary disease, particularly cryptogenic fibrosing alveolitis. Such patients are particularly suitable for this form of transplantation as the transplanted lung, more compliant and with a lower pulmonary vascular resistance, is preferentially ventilated and perfused after surgery.[15] Suitable patients are hypoxaemic at rest, become further desaturated with minimal exercise, and are unresponsive to conventional medical treatment. Previous surgery or some obliteration of the pleural space is not a contraindication. Not only can the less affected side be chosen but cardiopulmonary bypass is rarely necessary, so the risk of haemorrhage is less. Because the perioperative course is usually smoother than with heart-lung transplantation (and slightly more donor organs are available) patients up to the age of 60 can be accepted. The other selection criteria are the same as for recipients of heart-lung transplants.

The integrity and revascularistion[16] of the bronchial suture line is ensured by wrapping the anastomosis in a pedicle of greater omentum. It is, however, important to wean patients on to as low a dose of corticosteroids as possible before surgery to aid healing at this site. Other immunosuppressive treatment, such as azathioprine or cyclophosphamide, has been shown not to affect healing.[17] Medium term results are available from only one substantial series, from the Toronto group[18]; but a one year survival rate of 60% is to be expected. This will almost certainly improve to levels enjoyed by recipients of heart-lung transplants as experience increases.

Functional results are excellent, with restoration of gas exchange and an exercise capacity that allows a normal life style.[19] Single lung transplantation has manifest advantages, particularly for the patient with previous surgery, and it makes economical use of donor organs. The heart and both lungs from one donor can be used, permitting three recipients to benefit.[20] Despite these advantages, application is largely restricted at present to patients with end stage pulmonary fibrosis. Early experience of single lung transplantation in patients with emphysema was unsatisfactory, the transplanted lung becoming com-

pressed by the grossly overinflated contralateral lung.[21] There are, however, preliminary reports of the use of single lung transplantation in this setting more recently, with satisfactory early results.[22] Single lung transplantation is unlikely ever to be applied to patients with chronic lung infection, such as those with cystic fibrosis, because of the inevitable spread of infection from the contralateral lung in an immunosuppressed patient.

The future

Most of the unsolved problems in lung transplantation are common to both types of transplant. Lung preservation is in its infancy. Various methods have been reported, including flushing of the pulmonary bed with cold blood[23] or crystalloid[24] or core cooling of the donor with cardiopulmonary bypass.[25] These allow an ischaemic time of four to six hours. All result in some initial dysfunction, which usually recovers over the first few days. Future research will be directed towards reducing this lung injury, which shares many of the characteristics of the adult respiratory distress syndrome.

Opportunist infection is the greatest cause of mortality and morbidity in the first few months after transplantation. The particular importance of primary cytomegalovirus infection in the transplanted lung is now recognised.[26] It is largely avoided by appropriate matching of donor to recipient or, more expensively, by use of prophylactic cytomegalovirus hyperimmunoglobulin in non-matched patients. If infection does occur, the newer antiviral agent DHPG (gancyclovir) is of value.[26] Acute lung rejection may be diagnosed histologically from transbronchial lung biopsy specimens,[27] though the rejection process is clearly patchy and may lead to sampling error. The combination of transbronchial lung biopsy and bronchoalveolar lavage permits diagnosis of radiological infiltrates or a fall in pulmonary function in most patients after transplantation. Open lung biopsy is rarely required. The importance of serial pulmonary function testing in the detection of rejection and infection is recognised by most groups. Pulmonary rejection may occur in the absence of cardiac rejection,[28] and endomyocardial biopsy is of no value in diagnosing lung rejection.[29]

The most common cause of late morbidity and mortality is progressive airways obstruction, with a histological picture of obliterative bronchiolitis.[30] This has been described in up to 30% of long term survivors[31] and follows both heart-lung and single lung transplantation. It is probably a manifestation of chronic rejection[32] and would seem to be more common in patients who have had repeated early rejection episodes. It may also be triggered by viral

infection.[33] In the early stages it may be reversed by augmented immunosuppression.[34]

Future expansion of pulmonary transplantation will be limited by the number of donors and economical use of organs is of great importance. We may expect to see expansion of the role of single lung transplantation. Patients with respiratory disease who have adequately preserved cardiac function can participate in the so called "domino" procedure: when they receive a new heart and lungs their own heart can be used for a recipient of a heart transplant. The alternative approach of double lung transplant, preserving the recipient's own heart (and using the heart from the donor for another recipient)[35] achieves the same economy of donor organs, but it has met with problems of tracheal dehiscence and has now been largely abandoned in its original form (GA Patterson, personal communication).

Lung transplantation is at the same stage as cardiac transplantation in the early 1980s. The prospects for the next few years are very exciting.

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