Is lung retransplantation indicated?
Report on four patients

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ABSTRACT: As more lung transplantations are performed, many patients will suffer graft failure and will be considered for retransplantation. This article reviews the case management reports of four patients who received lung or heart/lung retransplantation, with overall disappointing results. The pros and cons of lung retransplantation are discussed.
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Lung transplantation can now be offered to many patients suffering from end-stage lung disease, with the expectation of a good outcome. Cystic fibrosis, emphysema, pulmonary fibrosis, pulmonary vascular disease and bronchiectasis are the most common indications for lung transplantation. One year survival for these patients is approximately 65%, and at two years it is approximately 56% [1].

Lung transplantation has not achieved the same success rate as other solid organ transplants, *e.g.* heart, liver and kidneys. Most of the early deaths occur due to technical difficulties, ischaemia related complications and infection; very few patients die from acute rejection. Bronchiolitis obliterans is the cause of death in most patients surviving for more than 6 months [2].

Retransplantation has been proposed as a therapeutic option for patients who have irreversible graft failure, either early after transplantation, or when bronchiolitis obliterans becomes advanced enough to render the chances of survival poor. This option raises questions regarding the expected outcome of retransplanted patients, and also has socio-economic and ethical considerations. Retransplanting lungs may drain already exhausted hospital budgets and deny those patients waiting for first grafts an opportunity to receive scarce donor lungs, with the possibility of better results.

In this article, we present four case reports of lung transplant patients who received second lung allografts. Outcome and problems related specifically to the issue of retransplantation are discussed. Data from the International Heart and Lung Transplant Registry (M. Kaye, San Diego, USA) are used to elaborate upon the global experience with lung retransplantation.

Case report 1

A 36 year old male, with alpha$_1$-antitrypsin deficiency, underwent enblock double lung transplantation on December 14, 1989. Both donor and recipient status were negative for cytomegalovirus (CMV). A donor-recipient cross-match was negative at 3 h. The Class I and II human leucocyte antigen (HLA) phenotypes were ((A29, A33) (B14, B44) (C -, -) (Dr1, Dr8) for the recipient) and ((A2, -) (B44, B62) (Cw3, -) (Dr4, -) for the donor). Mechanical ventilation was discontinued postoperatively, and the patient had an uneventful recovery except for the occurrence of grade 1 rejection on day 7. This was treated with augmentation of steroids with a good response.

The patient was discharged on the fifteenth postoperative day. His forced expiratory volume in one second/forced vital capacity ratio (FEV$_1$/FVC) improved from 0.5/2.3 preoperatively to 3/3.1 on the 21st postoperative day. By the 45th postoperative day, a slow decline in FEV$_1$ to 2.5 l was observed, despite increasing FVC up to 3.3 l. Transbronchial lung biopsy revealed no parenchymal abnormality. A left main bronchial stenosis was noted on bronchoscopy. This was successfully dilated and stented, with immediate improvement in FEV$_1$ and FVC to 4.1 and 4.3 l, respectively. The patient continued to be symptom free, with good lung function until 7 months post-transplant, when he went on a fishing trip and decided to reduce his cyclosporin dosage by half, in order to maintain his short supply for the duration of the trip. He returned a few days later in marked dyspnoea with pyrexia of 38°C. His clinical and radiological picture was consistent with acute rejection.

A transbronchial biopsy confirmed the presence of Grade III rejection. He responded well to pulse steroid therapy, and was discharged one week later with stable pulmonary function (FEV_1 and FVC 4.2 and 4.5 l, respectively). However, frequent recurrent episodes of acute rejection continued to occur. Nine months after transplantation, a histological diagnosis of bronchiolitis obliterans was made. The patients condition was now further complicated by recurrent episodes of pneumonia caused by Pseudomonas and Aspergillus. Thirteen months post-transplantation his FEV_1 measured 0.6 l and FVC 1.6 l. He now had a Grade III/IV dyspnoea and he spent most of his time in hospital for recurrent infections.

His case was presented to our lung transplant committee and a decision was taken to retransplant him. A lung donor of similar blood group was identified 14 months post-transplantation. Bilateral sequential lung transplants were performed. Ischaemia time for the new right lung was 3 h and 38 min, and for the left lung 5 h and 10 min, with what was perceived as adequate preservation and excellent donor lung condition prior to transplantation. Immediately following implantation, primary graft failure was noted, with evidence of high pulmonary vascular resistance, right ventricular dilatation and failure to come off cardiopulmonary bypass. This was associated with an arterial oxygen saturation of less than 50%, and end-tidal carbon dioxide levels of zero. The patient was supported with an arterovenous extracorporeal membrane oxygenator and Biomedicus pump over 18 h. Death was declared when metabolic acidosis and cardiac arrhythmias became incorrectable.

Case report 2

A 43 yr old previous drug addict, with pulmonary talcosis secondary to previous intravenous methadone abuse, underwent left single lung transplantation on April 17, 1989. The recipient's serum was negative for CMV, while that of the donor was positive. Recipient HLA phenotypes were ((A3, A31) (B35, B50) (C-, -) (Dr4, Dr7)). The donor's were ((A2, A31) (B7, B27) (Dr1, Dr4)). Ischaemia time was 105 min; however, preservation was felt to have been inadequate due to poor preparation of the preservative solution. Ischaemia/reperfusion injury was evident immediately after the operation, with arterial oxygen tension (Pao_2) on 100% oxygen 82 mmHg (10.9 kPa) and arterial carbon dioxide tension ($Paco_2$) 87 mmHg (11.6 kPa). This poor lung function continued over the next 10 days.

A decision was made to retransplant the opposite lung alone if an open biopsy of the first transplanted lung revealed potentially reversible ischaemic injury. Alternatively, a double lung transplant was performed if infection or irreversible injury was noted in the biopsied lung samples. On the tenth postoperative day, the patient underwent retransplantation on the opposite side only, since open biopsies on the left lung confirmed the presence of diffuse ischaemic alveolar damage and no infection. Again the operation was uneventful, with no need for cardiopulmonary bypass, and a lung from a donor with HLA of ((A2, A26) (B14, B44) (Dr2, Dr4)) was transplanted. This was successful, and early oxygenation appeared to be satisfactory (Pao_2 93 mmHg (12.4 kPa) and $Paco_2$ 45 mmHg (6.0 kPa) on 30% oxygen).

However, over the next four weeks, pyrexia associated with deteriorating arterial blood gases ensued. Cytomegalovirus, herpes simplex virus, *Candida albicans*, Staphylococcus and *Pseudomonas aeruginosa* pneumonia were documented at different times from bronchoalveolar lavage and lung tissue obtained by transbronchial biopsy. Multi-organ failure, including renal and liver dysfunction, thrombocytopenia, hyponitraemia and seizures ensued. The patient's death occurred one month after the second transplantation on 27 May 1989. Autopsy results revealed the presence of Pseudomonas bronchopneumonia and cytomegalovirus inclusion bodies in lung parenchyma. Invasive *Candida albicans* was found in both anastomoses. Organizing thrombi consistent with thromboembolism and patchy infarcts were noted in small and medium sized vessels in both lungs, and organizing bronchiolitis obliterans was also seen in the right lung.

Case report 3

A 36 yr old female noted a sudden onset of shortness of breath following pregnancy, and was diagnosed as having primary pulmonary hypertension in April 1987. She required supplemental oxygen, and by late 1987 was short of breath at rest and had advanced clinical right heart failure. Heart/lung transplantation was performed in January 1988, the donor being a 42 yr old female. The donor had HLA phenotypes ((A1, A2) (B57, -) (C6, C7) (Dr3, Dr7)). The recipient was ((A2, A30) (B18, B51) (Cw5,-) (Dr3, Dr7)). The transplant operation was complicated by intra-operative haemorrhage and a severe coagulopathy, requiring a prolonged intra-operative course and transfusion of more than 200 units of blood and blood products. The patient required moderate inotropic support and underwent sternal closure three days postoperatively, when the coagulopathy had finally resolved.

Her post-operative course was complicated by respiratory failure, renal dysfunction requiring dialysis for 10 days, and an episode of significant haematochezia due to CMV colitis. Bilateral pulmonary infiltrates were diagnosed as herpes simplex pneumonitis, since this virus was isolated on repetitive bronchoalveolar lavages. The patient also developed bilateral phrenic nerve paresis, as well as an extensive polyneuropathy, documented on electrophysiological testing. She underwent tracheostomy, and required mechanical ventilation for eight weeks. She was discharged home in April 1988, ambulatory and not requiring supplemental oxygen. Her pre-discharge pulmonary function tests revealed an FEV_1 of 1.5 l (44%), FVC 1.96 l (48%), slow vital capacity (SVC) 1.93 l (47%), inspiratory capacity (IC) 1.22 l (44%), expiratory reserve volume (ERV) 0.92 l (70%), and diffusing capacity of the lung for carbon monoxide (D_{LCO}) 9.05 ml·min^{-1}·kPa^{-1} (28%).

The patient's subsequent course was characterized by recurrent lower respiratory tract infections, necessitating hospitalization every two months, short-term in-hospital intravenous antibiotic therapy, and long-term oral suppressive antibiotic treatment. Repeated cardiac biopsies revealed no evidence of cardiac rejection, and transbronchial biopsies initially showed only interstitial fibrosis. Assessment one year following operation revealed normal cardiac function and no evidence of coronary artery disease on angiography. From January to June 1989, the patient developed multiple episodes of acute lung rejection, requiring augmented steroid therapy and OKT3. By June 1989, she was short of breath on exercise and transbronchial biopsies revealed obliterative bronchiolitis. By October 1989, her FEV_1 had declined to 0.57 l (18%) and FVC to 1.85 l (44%). Flexible bronchoscopy revealed diffuse bronchomalacia, involving all airways beyond the tracheal anastomosis. Over the next eight months, the patient required monthly rehospitalization for Pseudomonas tracheobronchitis. She was listed for a second heart/lung transplant in April 1990.

A heart/lung retransplant was performed on June 19, 1990, the donor being a 23 yr old CMV negative patient, with HLA phenotypes ((A3, A24) (B7, B39) (C-, -) (Dr6, Dr9) (Drw52, Drw53)). The total ischaemic time for the heart/lung graft was 80 min, and the total cardiopulmonary bypass time 308 min. The patient required 8 units of packed cells intra-operatively. Pathological examination of the original heart/lung graft revealed no significant cardiac abnormality, and normal coronary arteries. The lungs were grossly bronchiectatic and, on microscopy, acute and chronic lung rejection and terminal obliterative bronchiolitis were noted. Diffuse destruction of bronchial cartilage in the absence of adjacent infection was observed, along with grade III/VI Heath-Edwards pulmonary hypertensive changes.

The patient's Intensive Care Unit (ICU) course following her second transplant was more benign than after her first operation. She required one reoperation for coagulopathic bleeding, but was extubated on the ninth postoperative day. On the ward, she developed a persistent left upper lobe infiltrate, the cause of which could not be diagnosed, despite multiple transbronchial biopsies. A left open lung biopsy was performed four weeks postoperatively, showing only interstitial fibrosis in the region of the lung infiltrate. The patient was discharged six weeks postoperatively and did well for four months.

The patient returned in December 1990 with severe recurrent episodes of headache. Magnetic resonance imaging (MRI) scanning was negative, but lumbar puncture demonstrated cloudy cerebrospinal fluid, which grew *Candida albicans*. She was successfully treated with regular and liposomal amphotericin B. In January and April 1991, the patient was noted to have acute lung rejection, with lymphocytic bronchitis on follow-up transbronchial biopsies, and her immunosuppression was cautiously increased. At present, bronchial washings demonstrate only normal respiratory tract flora and occasional Candida. Her FEV_1 is 1.28 l (40%), FVC 2.02 l (55%),

FEV_1/FVC ratio 64%, SVC 1.94 (53%), residual volume (RV) 1.07 l (62%), total lung capacity (TLC) 3.01 l (55%), and $DLCO$ 9.42 $ml \cdot min^{-1} \cdot mmHg^{-1}$ (30%). Her Pao_2 and $Paco_2$ on room air are 73 and 30 mmHg (9.7 and 4.0 kPa), respectively, and on pulse oximetry her oxygen saturation decreases to less than 90% after only 10 min of exercise. She leads an active life out of hospital, but is dependent on Fiorinal for frequent headaches. Sixteen months following heart/lung retransplantation, she remains in a functional Class II condition.

Case report 4

A 56 yr old male with idiopathic emphysema had a right single lung transplanted in April 1990. His preoperative FEV_1 and FVC were 0.3 and 0.6 l, respectively. He received a lung from a 41 yr old motor vehicle accident victim, with a similar blood group A. Both donor and recipient serum were negative for cytomegalovirus antibody titres. The patient was removed from mechanical ventilation 17 h post-operatively, and had oxygen saturation of over 96% on room air within 10 days of surgery.

Two weeks following surgery, the patient developed a severe necrotizing herpetic bronchitis, which affected the right bronchus intermedius and lower lobe bronchus. This was controlled with a 3 week course of *i.v.* acyclovir 10 $mg \cdot kg^{-1}$ *q.d.* Unfortunately, the right bronchus inter-medius healed with a marked stricture necessitating laser dilatation and stent insertion. Despite a temporary mild improvement in FEV_1 from 0.9 to 1.2 l following stent insertion, distal airway disease progressed with a drop in FEV_1 to 0.6 l within 1 yr from transplantation.

The patient was put on the transplantation list again and 16 months after the first transplant, he received a second graft, this time on the contralateral side. As with the first graft, this did not require cardiopulmonary bypass. As the second donor was CMV negative and the recipient had now converted to CMV positive status, prophylactic CMV hyperimmunoglobulin was administered. The patient was extubated 25 h following surgery and had an uneventful recovery. Three weeks postoperatively, on the day of planned discharge, the patient developed three episodes of coughing white blood-streaked sputum. This was associated with a decline in O_2 saturation from 96 to 90% on room air. On chest roentgenogram, a faint alveolar-type infiltrate was noted in the left lower lobe. The differential diagnosis included pulmonary embolism, severe bronchitis, atrial thrombosis or bleeding from bronchial anastomotic necrosis. Among the planned investigations were bronchoscopy, cardiac ultrasonography and a pulmonary angiogram. The patient developed a massive bout of haemoptysis in the angiography suite, and could not be resuscitated. Autopsy revealed the presence of micro-perforation between the pulmonary artery and a partially necrotic bronchial anastomosis. The first lung allograft showed pulmonary fibrosis and diffuse bronchiolitis obliterans. The stent was intact with no evidence of infection.

Discussion

The early survival rate after lung and heart/lung transplantation continues to improve. Current 1 yr survival for heart/lung, double lung and single lung transplantation recipients is approximately 65% [1]. Advances in surgical technique, perioperative care, and the management of infection and acute rejection have contributed to the improvement in results. Unfortunately, at least 25% of lung transplant recipients continue to be at risk of early graft failure and death (within 3 months of transplantation) due to infection, acute rejection and airway complications [1, 3, 4]. Furthermore, the initial reduction in incidence of obliterative bronchiolitis in isolated lung allografts compared to that reported in the early heart/lung transplant literature, is no longer apparent [5]. Chronic rejection and bronchiolitis obliterans, complicated with infection, probably with *Pseudomonas aeroginosa* and Aspergillus, are now affecting a considerable number of our lung transplant recipients who have survived beyond the first year [6, 7].

For those in whom graft function deteriorates severely, and for whom an ideal medical therapy is not available, the option of retransplantation remains a consideration surrounded by controversy. Transplantation committee members spend hours debating whether a particular patient with end-stage bronchiolitis obliterans should or should not be transplanted, and frequently none of the arguments can be supported or refuted on scientific grounds.

Is lung or heart/lung retransplantation a worthwhile endeavour? Current information from the International Heart and Lung Transplantation Registry indicates that of 75 retransplant recipients registered, only 25 are alive at any time between 5 days and 4 years from retransplantation (33%). Most have died within the first 3 months after retransplantation (40 out of 50 patients).

The timing of retransplantation, a reflection of whether the primary graft failed early or late, had no impact on outcome. Eighteen out of 27 early retransplants (within 3 months of first graft) and 30 out of 45 late graft recipients died. Furthermore, the type of retransplant, whether single, double, or heart/lung made no difference. Twenty eight out of 38 heart/lung retransplant recipients died. All five single or double lung recipients who received heart/lungs as their second operation died. Twelve out of 17 single lung retransplant recipients died, and 6 out of 8 heart/lung or double lung recipients who received single lung retransplants died.

Technical difficulties and acute infection and rejection continue to afflict retransplant patients during the first month after surgery. More importantly, it is suggested that the host is likely to be less tolerant to the retransplant lungs. Experience from other organ retransplantations appears to substantiate that retransplanted allografts are more readily rejected than the initial transplants [8–10].

The choice of operation and techniques to be used must not be based on dogma, and should be tailored to the specific needs of the particular case. Pre-operative assessment of cardiac function, and the level of bronchial anastomosis, should determine the choice between heart/lung or double lung retransplantation. When cardiac dysfunction or advanced coronary atherosclerosis is present, heart/lung transplantation should be considered. Similarly, when the bronchial anastomosis is high, there may be some merit in considering a tracheal anastomosis with a heart/lung preparation as opposed to a double lung transplant, which carries a higher risk of tracheal anastomotic dehiscence. Single lung transplants, on the other hand, are likely to be amenable to a second single lung transplant on the same or opposite side, depending on the infectious condition of the old lung.

More information is clearly required. This should include data on characteristics of the donor and recipient, including the HLA typing of first and second donors and recipients, methods of preservation postoperative development of ischaemic injury, infection and rejection, and immunosuppressive protocols used early and long-term. A specific procedure should be advocated for particular indications (*e.g.* single lung retransplant for non-infected double lung allograft failure, heart lung or double lung for infected double lungs). Once this is agreed upon, it must be tested in a large multicentre trial. Survival and functional outcome should be evaluated in a phase II trial and, if ethically warranted, should later be tested in another trial, which contains another group of patients who will not be subjected to retransplantation. Without this, we will continue to waste lives, time and precious donor lungs.

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