MEDICAL PRACTICE

Contemporary Themes

Heart and lung transplantation in patients with end stage lung disease

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Abstract

Combined heart and lung transplantation was used to treat seven patients with end stage lung disease. All were severely disabled, and their disease carried a poor prognosis. Six patients were well four to 33 months after transplantation. One patient died after 44 days from a primary cytomegalovirus pneumonia transmitted from the donor. All the survivors had normal exercise tolerance and greatly improved lung function.

It is concluded that heart and lung transplantation is a suitable treatment for selected patients with end stage chronic lung disease.

Introduction

Human heart and lung transplantation was first reported in 1982.[1] The patients had severe pulmonary vascular disease, either primary or secondary to cardiac disease.[2,3] Despite the long term problems in diagnosing rejection or infection in the transplanted lung,[2-4] this treatment may be beneficial for patients with other lung diseases. We report our early experience of combined heart and lung transplantation in seven patients who had end stage chronic lung disease.

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Methods

Between November 1982 and September 1986, 199 patients were referred for heart and lung transplantation. Of these, 53 patients were accepted on to a waiting list and 19 received a transplant. Seven of these patients had chronic lung disease. All 199 patients were severely disabled. Those who were selected for transplantation had a poor prognosis, and no further conventional treatment could be offered to them. Patients were accepted for operation if they were under 49 years of age and free of systemic illness or secondary organ dysfunction. Other contraindications were previous extensive cardiac or thoracic surgery,[3] the presence of systemic infections, or concurrent treatment with corticosteroids.

Table I gives the ages of the seven patients (range 20 to 43 years) and the diagnoses. They had been ill for from two to nine years. Two were confined to bed in hospital, and the others required frequent treatment as inpatients. As a group the maximum reported exercise tolerance was walking a distance of 100 yards (91·4 m) on the flat at their own pace (table I).

TABLE I—*Details of heart and lung transplant recipients before operation*

Patient No	Age (years)	Sex	Diagnosis	Secondary right heart failure	Maximum exercise tolerance
1	37	F	Cryptogenic fibrosing alveolitis	Yes	Confined to bed
2	20	F	Cystic fibrosis	Yes	30 yards (27·4 m)
3	42	F	Emphysema	Yes	Confined to bed
4	35	F	Sarcoidosis	Yes	30 yards (27·4 m)
5	47	F	Emphysema	Yes	40 yards (36·6 m)
6	23	M	Histiocytosis X	No	20 yards (18·2 m)
7	43	M	Bronchiectasis	Yes	100 yards (91·4 m)

Only the patient with cystic fibrosis had infected sputum at the time of the operation. The organism consistently cultured from the sputum was *Pseudomonas aeruginosa*. The patients with cryptogenic fibrosing alveolitis, histiocytosis X, and sarcoidosis had been treated with corticosteroids and azathioprine in the past. All patients with airways obstruction were treated with inhaled bronchodilator (salbutamol) and inhaled topical steroid (beclomethasone diproprionate).

The diagnoses of cryptogenic fibrosing alveolitis and histiocytosis X were made by open lung biopsy at the referring hospital. Sarcoidosis was diagnosed from a lymph node biopsy specimen. The diagnosis in the other patients was confirmed from histology of the lungs after transplantation.

The operation (fig 1), selection of donors, and perioperative care have been described elsewhere.[5] Immunosuppressive treatment was given with cyclosporin and prednisolone to the first patient; the other six received cyclosporin and azathioprine. Pulmonary function was recorded before and after the operation, at monthly intervals for six months, and every five months thereafter. A dry wedge spirometer was used to record forced expired volume in one second and forced vital capacity (Vitalograph, Buckingham, England). Single breath gas transfer for carbon monoxide was measured with Transfer Test equipment (P K Morgan, Chatham, Kent, England).[6] Static lung volumes were recorded in a whole body plethysmograph (P K Morgan, Chatham, Kent, England).[7]

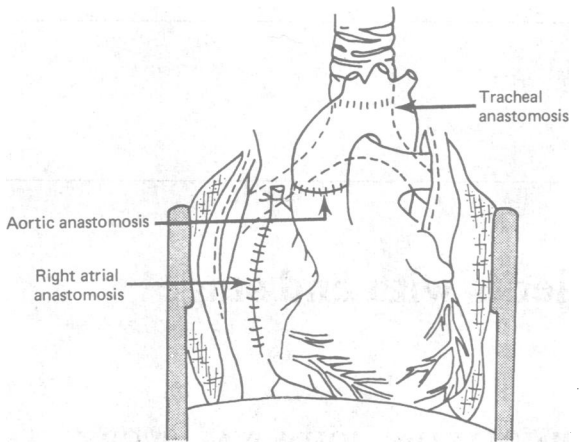

FIG 1—Diagram of heart and lung transplantation, showing the tracheal anastomosis about 1·5 cm above the carina and the atrial and aortic anastomoses between the recipient's remaining right atrium and ascending aorta to the donor heart. The phrenic nerves are carefully preserved within a pedicle of pericardium.

Results

All the patients survived the operation. One died after 44 days from cytomegalovirus pneumonitis diagnosed after a transbronchial lung biopsy. All of the other patients are alive four to 33 months after their operation.

Table II lists the postoperative complications. Only one patient required assisted ventilation for more than 36 hours after the operation (patient 3), largely because of chest wall deformity, pectus carinatum, and kyphoscoliosis. Patient 7 had a recurrent chylous effusion that required continuous pleural drainage for three weeks.

Patient 1 survived a severe primary cytomegalovirus infection of the small bowel that was diagnosed serologically and by culture of a gastric mucosal biopsy specimen. Patient 7 had a mild febrile illness within a week of the operation which was associated with a rise in specific IgM to cytomegalovirus but had no other disorder. His fever resolved after treatment with hyperimmune globulin. These two patients and the patient who died were seronegative for cytomegalovirus before the operation but received organs from seropositive donors. Another such patient suffered no ill effects and remained seronegative for cytomegalovirus.

Three patients (1, 2, and 5) had a bacterial bronchial infection, one at seven days, one at three months, and patient 1 had two infections at six and nine months. They all had a cough, sputum, and fever, and no radiological abnormality. The diagnosis was made by sputum culture, which showed *Streptococcus pneumoniae* in two and *Haemophilus influenzae* in the other. They responded to oral amoxycillin 500 mg three times a day. During the illness small changes in forced expired volume in one second and forced vital capacity occurred, but there was little change in gas transfer for carbon monoxide or total lung capacity. A tuberculous empyema developed in patient 1, who had been treated for tuberculosis in 1971. This responded to a standard course of rifampicin, isoniazid, and ethambutol.

Patient 1 also had an episode of rejection which coincided with the start of antituberculous chemotherapy. The diagnosis was made clinically.[3,8] The patient complained of increasing breathlessness; there were no interstitial shadows in the radiograph, but she had widespread late inspiratory crackles on auscultation of the chest. In addition, the forced expired volume in one second and forced vital capacity fell. This episode responded to a three day course of intravenous methylprednisolone (3 g) and a temporary increase in the dose of cyclosporin (fig 2).

Lung function improved progressively in all six survivors (fig 3). Three returned to work four to six months after the operation, and the other three

TABLE II—*Postoperative course of seven patients with primary lung disease who had heart and lung transplantation*

Patient No	Length of hospital stay (days)	Complications of operation	Rejection episodes	Infection episodes	Survival to 1 Jan 1987 (months)
1	78	None	One	Primary cytomegalovirus infection; reactivated tuberculosis; RTI	33
2	36	None	None	RTI	15
3	84	Bleeding from SVC site and difficulty in weaning from ventilator; tracheostomy; chest wall deformity	None	None	15
4	44	None	None	Cytomegalovirus pneumonitis	Died day 44
5	36	None	None	RTI	7
6	42	None	None	None	7
7	62	Right chylothorax		Primary cytomegalovirus infection	4

RTI=Respiratory tract infection with fever, productive cough, identifiable pathogens in sputum and a response to antibiotics.
SVC=Superior vena cava.

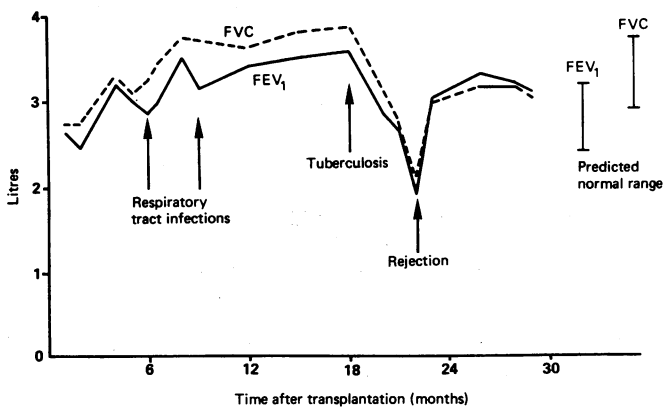

FIG 2—Forced expired volume in one second (FEV_1) and forced vital capacity (FVC) in patient 1 measured over 33 months; predicted values are shown by the lines and bars. Changes in dynamic lung volumes are shown at times of infections and during episode of rejection.

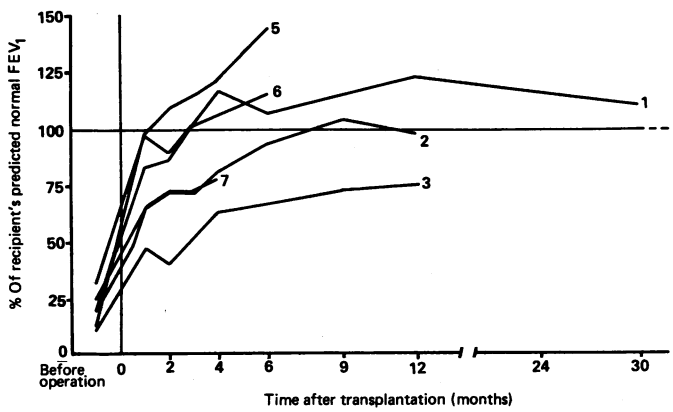

FIG 3—Forced expired volume in one second (FEV_1) as percentage of predicted for each surviving patient before operation and during months after operation.

were fit to do so. Before transplantation all patients had reduced values of forced expired volume in one second of between 11% and 22% of those predicted. With the exception of patient 3, who had a chest wall deformity, all patients achieved 80% of predicted values by four months and 100% by six months. The increase in forced expired volume in one second was greater than the increase in forced vital capacity, which, however, took about the same length of time to improve. Apart from patient 3 all other survivors achieved a total lung capacity of 90-100% of predicted values by four months. The gas transfer for carbon monoxide also rose to a range of 89-98% of predicted values by four months.

At six months all of the patients could walk any distance at a normal walking pace. The results of formal exercise tolerance tests will be reported later.

Discussion

Combined heart and lung transplantation was initially used to treat pulmonary vascular disease. Since 1984, 19 heart and lung transplants have been performed at this hospital, seven of them for chronic lung disease. Our limited experience with these seven patients indicates that with suitable selection this is a worthwhile treatment. With time lung function has returned to normal predicted values, and patients report normal exercise tolerance. In contrast to patients with pulmonary vascular disease our survivors have not developed obliterative bronchiolitis.[3 8] A recent review places lung transplantation for lung disease in perspective.[9] Success, however, has lagged behind that with other organs for various reasons.

Our major clinical problems have been cytomegalovirus infection and rejection. The cytomegalovirus infections were primary, occurring shortly after the operation, and are assumed to have been acquired by previously seronegative recipients from the donor.[10] This has led to a change in practice. Donors are now serotyped for cytomegalovirus, and the recipient is matched. In future it may be possible to "vaccinate" the seronegative recipients for cytomegalovirus to extend the potential range of donors.

In one patient a serious rejection episode followed the start of antituberculous treatment. As antibiotics are known to reduce the efficacy of cyclosporin[11] the event was expected. A full response to increased immunosuppression, including relief of symptoms, the disappearance of abnormal physical signs, and an increase in pulmonary function, was observed after 14 days of treatment.

Bacterial bronchitis occurred on three occasions but responded to treatment with conventional antibiotics, and there was no sustained loss of lung function. Three factors may have contributed to these infections: a reduction in the efficacy of the cough reflex, impaired mucociliary clearance, and interruption of the mucociliary "escalator" at the tracheal anastomosis. These patients can cough because the larynx and trachea are innervated.[5] The airways below the anastomosis, however, are denervated, preventing the initiation of the cough reflex from the bronchial tree. Mucociliary clearance may also be impaired in these regions as a result of denervation,[12 13] although this has not yet been studied. The interruption of the mucociliary escalator at the tracheal anastomosis may also be important.

The size of the donor lungs and the recipient's thoracic cavity must be matched. If the donor lungs are too large atelectasis and right to left shunt may occur.[4] We measure thoracic vertebral height and width of the rib cage in the chest radiograph. Three recipients had overinflated lungs, two of whom had emphysema and one of whom had histiocytosis X. All had a normal total lung capacity after operation (96-108% of recipient values predicted by four months).

Patients with pulmonary vascular disease who undergo heart and lung transplantation have a restrictive ventilatory defect.[14] This probably reflects changes in the mobility of the chest wall after median sternotomy,[15] which is also seen in patients after coronary artery bypass grafting and which resolves with time.[16] This effect was less obvious in our patients, in whom preoperative lung function was grossly reduced. All patients achieved a normal total lung capacity four months after the operation.

Combined heart and lung transplantation for lung disease may not be superior to transplantation of both lungs or of a single lung.[17] It is easier to transplant the heart and lungs together.[4] But it is no longer thought that the transplanted heart offers a means of diagnosing rejection through an endomyocardial biopsy.[18] The transplanted heart and lungs reject independently of one another.[19]

Single lung transplantation is valuable for fibrotic lung disease,[20] but earlier experience with a wide range of lung disease was disappointing.[21] This reflects the poorer healing of a bronchial anastomosis compared with a tracheal anastomosis, which has a better collateral blood supply.[22] Patients who have suppurative lung disease will infect the transplanted single lung, and ventilation and perfusion mismatch may occur in emphysema.[23] Our experience suggests that combined heart and lung transplantation should therefore be offered to these patients. Only patient 1 would have been suitable for single lung transplantation.

To gauge the potential recipient population we reviewed the mortality for England and Wales from these chronic lung diseases in patients between the ages of 10 and 49 years (table III). Cryptogenic fibrosing alveolitis is a disease of elderly people so that only a few are within our age range. Similarly, only a few patients die from sarcoidosis and other "granulomatous" lung diseases. Some patients under 49 years of age who die with emphysema will have α_1 antitrypsin deficiency,[24] although neither of our patients in this series had the condition. Theoretically, α_1 antitrypsin deficient recipients may be prone to develop emphysema in the transplanted lungs during periods of pulmonary inflammation,[25] such as might occur with episodes of infection or rejection.

TABLE III—*Deaths from respiratory disease in England and Wales for ages 10 to 49 years*

Year	Diagnosis					Total No of potential heart and lung transplant recipients
	Cystic fibrosis	Emphysema	Sarcoidosis	Fibrosing alveolitis	Other lung diseases*	
1979	81	36	20	13	13	163
1980	88	29	15	20	17	169
1981	87	26	14	9	27	163
1982	55	29	24	15	22	145
1983	101	26	22	13	19	181
1984	92	32	27	21	13	185

*Includes collagen vascular disorders and pulmonary eosinophilia.

More patients with cystic fibrosis than with other diseases are likely to benefit from combined heart and lung transplantation, particularly as most now survive until adult life.[26] Selection is important; relative contraindications would be extrapulmonary disease—for example, insulin dependent diabetes mellitus, which occurs in 4% of patients, and liver disease with portal hypertension, which is present in 1%.[27] It is now possible, however, to combine transplantation of the liver with transplantation of heart and lungs. Extensive pleural fibrosis from surgical treatment of recurrent pneumothorax may be an important contraindication. Recurrent pneumothorax is common in the older patients with cystic fibrosis.[28] Pulmonary infection in cystic fibrosis is not a problem since it is usually confined to the lungs. Pleural and systemic infections are rare.[29] Transplantation offers the removal of the main source of sepsis. In our patient it was associated with an increase in body weight of 6 kg in the first 12 weeks. The presence of *Aspergillus fumigatus* is of concern as a possible opportunistic infection after transplantation.[30]

We conclude that probably about 100 patients a year with lung disease in England and Wales would benefit from combined heart and lung transplantation. This should not be too great a demand on donor resources but implies that several centres need to carry out this type of surgery. There is still the problem of diagnosis and treatment of rejection.[3] Transbronchial lung biopsies may help to solve this, and our experience of this technique will be reported. In addition, there remain difficulties in using cyclosporin, particularly in determining adequate treatment for the patient and avoiding nephrotoxicity.[31] Nevertheless, our limited experience of heart and

lung transplantation is encouraging. This surgery offers a treatment for a wide range of end stage chronic lung disease.

We thank Mr Ben Milstein for editorial comments and criticisms; Ms Noreen Caine for the mortality statistics; Professor M Turner-Warwick, Dr J C Batten, Dr M E Hodson, Dr S W Clarke, Dr G M Jeremiah, Wing Commander W Hopkirk, and Dr M M Webb-Pearce for referring patients; the staff at the hospitals from which we obtained donor organs for their help; and Miss K Lightfoot for preparing the manuscript.

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(Accepted 15 April 1987)

Third World Issues

Epidemiological assessment of the health and nutrition of Ethiopian refugees in emergency camps in Sudan, 1985

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Abstract

The findings from epidemiological data that were collected from emergency camps for Ethiopian refugees during a mass influx of refugees into Eastern Sudan in 1985 are presented. An overall mortality of 8·9 per 10 000 a day was recorded during February 1985, and in children under 5 years of age the rate was 22 per 10 000 a day. The estimated prevalence of malnutrition (calculated as less than 80% of the reference weight for height) ranged from 32% to 52% among children of preschool age. The principal causes of morbidity and mortality were measles, diarrhoea and dysentery, respiratory infections, and malaria.

The findings suggest that malnutrition and disease increased in these refugees after they arrived in the camps. Epidemiological assessment is essential to help to maintain the health and nutrition of refugees in emergency camps.

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Introduction

Refugee emergencies are characterised by rapid mass migration and subsequent establishment of relief camps that are often large and unplanned. Because of the suddenness of such occurrences there may be insufficient water, food, and shelter in these camps, causing malnutrition and disease in the affected populations.[1] The earliest medical response is often prompted by emotive media reports and not by epidemiological assessment, resulting in an overemphasis on