Early experience of heart-lung transplantation

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SUMMARY We report our experience of heart-lung transplantation for the treatment of children with terminal respiratory disease. Between May 1987 and October 1988 we performed heart-lung transplantation in five children under the age of 16 (age range 11–15). All the patients were severely disabled by dyspnoea and hypoxia. Two had primary pulmonary hypertension, two cystic fibrosis, and one had Eisenmenger’s syndrome.

All five children are alive and well five to 17 months after operation and have returned to activities normal for their age. Three of the five patients had episodes of infection after operation. These were staphylococcal pneumonia, herpes simplex pneumonitis and, in one of the patients with cystic fibrosis, persistent purulent sputum. The mean number of episodes of rejection per child was 2·7 per half year. Heart-lung transplantation is a practical treatment for children in these disease groups with terminal respiratory failure.

In 1981 after the introduction of cyclosporin and the development of a new surgical technique, heart-lung transplantation began to yield satisfactory results. First introduced as a treatment for pulmonary vascular disease, heart-lung transplantation was extended to treat end stage lung disease and then cystic fibrosis. Since 1984 we have performed 51 heart-lung transplantations. As experience increased and survival improved recipient selection was expanded to include older and younger patients. We report here our experience in five children under the age of 16 years (range 11–15 years) who had a heart-lung transplantation between May 1987 and October 1988.

Patients and methods

Between March 1985 and October 1988, 33 children below the age of 16 were referred for assessment of their suitability for heart-lung transplantation. Thirty of these have been assessed and 15 were placed on the active waiting list for transplantation. Ten were considered to be suitable but not sufficiently disabled to require transplantation and were placed on a 'provisional' waiting list. Five patients were felt to be unsuitable, four because they were too well and the other because of profound intellectual difficulties. Two of the 10 patients for whom donor organs did not become available died, both within two months of assessment, and four patients died waiting to be assessed. Suitable donor organs became available for five of the 15 patients accepted.

Preoperative assessment included determination of the degree of disability, including requirement for home oxygen, evidence of other organ malfunction, and the presence of right ventricular failure. Respiratory function testing included spirometry (Vitalograph Ltd), single breath transfer for carbon monoxide (P K Morgan), measurement of lung volumes by whole body plethysmography (Jaeger Bodyscreen II Body Box, Eric Jaeger GmbH and CoKG), and helium dilution (Spectromed Ltd). All patients underwent a 12 minute walk with continuous arterial oxygen saturation measurement using pulse oximetry (Datascope Accusat Pulse Oximeter, Datascope). The 12 minute walking distance was measured together with the minimum arterial oxygen saturation achieved during this exercise.

Donor and recipient matching was, in the first instance, by ABO blood group compatibility and cytomegalovirus antibody status. The donor and recipient were matched for size by taking measurements of the height of the thoracic vertebral column and width of the rib cage on the chest radiograph.

Donor lungs were considered suitable if they had normal compliance (peak inspiratory pressure below
2.67 kPa, tidal volume of less than 15 ml/kg, respiratory rate of between 10 and 14 breaths/minute), normal gas exchange (arterial partial pressure of oxygen greater than 15 kPa with fractional inspired oxygen of 30%), and no evidence of pulmonary infection. As these criteria are so precise less than 20% of heart donors are acceptable as lung donors.7

The technique for heart-lung transplantation has been previously described.8 9 All grafts were distantly procured at the donor hospital. The ischaemic times were 150–188 minutes. Immunosuppression was maintained with oral cyclosporin and azathioprine. The dose of cyclosporin was adjusted to give a whole blood concentration of less than 1000 µg/ml, a plasma concentration less than 300 µg/ml, and a concentration of azathioprine to keep the total white cell count above 5.0 x 10^9/l. Rejection episodes were treated with intravenous methylprednisolone 500 mg, daily for three days followed by oral methylprednisolone 1 mg/kg/day reducing to 5–10 mg/day over a period of 10 days. Patients remained on this dose until the episode of rejection was deemed on clinical or histological grounds, or both, to have resolved.

Postoperatively patients were monitored clinically, radiologically, and by pulmonary function. A microspirometer (Micromedical Ltd) was used to record forced expiratory volume in one second (FEV1) (figure). Fever, dyspnoea, crackles on auscultation, radiologic shadows, and a fall in FEV1, suggesting lung rejection or infection, were an indication to perform fibreoptic bronchoscopy and transbronchial biopsy.10–12 Routine transbronchial biopsy was performed at three months and then yearly after operation. Routine endomyocardial biopsies do not contribute to patient management and were not performed.13 Rejection was distinguished from infection by the presence of perivascular lymphocytic infiltrates.11 Viral pneumonitis was confirmed histologically by the presence of diffuse alveolar damage in association with viral inclusion bodies.10

Results

Preoperative details of the five patients who received heart-lung transplants are shown in table 1. The FEV1 measured was compared with values predicted for sex and height in children.14 All patients were severely disabled with a 12 minute walking distance of less than 350 metres. Both patients with cystic fibrosis required continuous oxygen treatment and had evidence of right ventricular failure requiring diuretic treatment. There was no evidence of renal or hepatic dysfunction and fasting blood glucose concentrations were normal in all cases. The three patients with pulmonary vascular disease had cardiac catheterisation performed as part of their assessment. All had raised pulmonary artery pressure and reduced cardiac output (table 2).

The preoperative diagnosis in patient 2 was thought to be Eisenmenger’s syndrome secondary to an ostium primum atrial septal defect. On examination of the explanted organs no intracardiac shunt was shown and a diagnosis of primary pulmonary hypertension was made.

Mean time from acceptance onto the waiting list and transplantation was 2–4 months. The predicted total lung capacity for the donor14 and the measured total lung capacity for the recipient showed that satisfactory size matching was achieved (table 3). Postoperative complications are shown in table 4. Patient 1 was weaned off cardiopulmonary bypass with difficulty because of left ventricular dysfunction possibly associated with a subendocardial infarction in the donor heart. The heart failure was refractory to β agonists, but enoximone (Merrell Dow Pharmaceuticals Ltd), a phosphodiesterase inhibitor, restored haemodynamic stability and there were no long term cardiovascular sequelae. The early postoperative course in patient 4, who had had two previous thoracotomies, was complicated by recurrent bleeding necessitating surgical intervention on three occasions. Serial spirometric studies showed an early postoperative fall in FEV1 (figure), which subsequently rose, as in patient 2, to around 100% predicted value. In patients 1 and 3 this increase in FEV1 was delayed by episodes of rejection. There was a mean of 2–7 episodes of rejection per child per six months.
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Table 1  Details of sex, diagnosis, and age at time of transplant, and assessment details for each patient treated with heart-lung transplantation

<table>
<thead>
<tr>
<th>Patient No (sex)</th>
<th>Diagnosis</th>
<th>Age at transplant</th>
<th>FEV₁ (% predicted)</th>
<th>Blood gases in air (kPa)</th>
<th>Distance walked (metres)</th>
<th>Lowest arterial oxygen saturation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (M)</td>
<td>Primary pulmonary hypertension</td>
<td>12</td>
<td>64</td>
<td>*</td>
<td>*</td>
<td>310</td>
</tr>
<tr>
<td>2 (F)</td>
<td>Primary pulmonary hypertension</td>
<td>15</td>
<td>53</td>
<td>*</td>
<td>*</td>
<td>Unable to perform walk</td>
</tr>
<tr>
<td>3 (F)</td>
<td>Cystic fibrosis</td>
<td>11</td>
<td>16</td>
<td>7:2</td>
<td>7:2</td>
<td>240</td>
</tr>
<tr>
<td>4 (F)</td>
<td>Eisenmenger's syndrome</td>
<td>15</td>
<td>66</td>
<td>5:4</td>
<td>3:8</td>
<td>300</td>
</tr>
<tr>
<td>5 (F)</td>
<td>Cystic fibrosis</td>
<td>14</td>
<td>19</td>
<td>7:4</td>
<td>5:9</td>
<td>260</td>
</tr>
</tbody>
</table>

*Data not available.

Table 2  Data from cardiac catheterisation on three patients with pulmonary vascular disease

<table>
<thead>
<tr>
<th>Patient No</th>
<th>1</th>
<th>2</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time before transplantation (months)</td>
<td>3</td>
<td>18</td>
<td>1</td>
</tr>
<tr>
<td>Mixed venous oxygen saturation (%)</td>
<td>57</td>
<td>59</td>
<td>55</td>
</tr>
<tr>
<td>Mean pulmonary artery pressure (kPa)</td>
<td>13-50</td>
<td>9:33</td>
<td>6:7</td>
</tr>
<tr>
<td>Cardiac index (l/min/m²)</td>
<td>1:9</td>
<td>1:1</td>
<td>1:9*</td>
</tr>
</tbody>
</table>

*Pulmonary flow index.

Table 3  Total lung capacity (in litres), measured by whole body plethysmography (patients 1–4) and by helium dilution (patient 5), predicted and measured for each recipient compared with the predicted total lung capacity¹ for each donor

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Recipient</th>
<th>Donor-predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Predicted</td>
<td>Measurement</td>
</tr>
<tr>
<td>1</td>
<td>3:68</td>
<td>3:8</td>
</tr>
<tr>
<td>2</td>
<td>4:46</td>
<td>4:0</td>
</tr>
<tr>
<td>3</td>
<td>2:78</td>
<td>3:41</td>
</tr>
<tr>
<td>4</td>
<td>3:59</td>
<td>2:97</td>
</tr>
<tr>
<td>5</td>
<td>2:73</td>
<td>1:93</td>
</tr>
</tbody>
</table>

The first patient was cytomegalovirus antibody negative, but received organs from a donor who was positive as the result of a false negative latex agglutination test performed at the donor hospital. He was given prophylactic hyperimmune globulin when the mismatch was identified. On day 32 he developed increasing shortness of breath and a decline in respiratory function tests (figure). Cytomegalovirus pneumonitis was suspected, a transbronchial biopsy was performed and he was treated with the antiviral agent ganciclovir (Cymevene, Syntex). Histological examination showed evidence of acute rejection without any of the typical changes of cytomegalovirus pneumonitis. He was then treated for rejection, which resulted in symptomatic improvement and a rise in FEV₁. There was no rise in antibody to cytomegalovirus, and viral cultures were negative.

Patient 4 presented on day 50 with florid herpes simplex lesions in the mouth, a spiking temperature, and radiographic features of pneumonitis. The specimen obtained at transbronchial biopsy, although not specific for herpes simplex pneumonitis, showed viral pneumonitis and the patient responded promptly to treatment with intravenous acyclovir.

Patients 4 and 5 had evidence of growth delay preoperatively; heights were below the 10th centile

Table 4  Postoperative complications

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Early postoperative complications</th>
<th>Episodes of infection</th>
<th>No of episodes of rejection*</th>
<th>Time since heart-lung transplantation (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Left ventricular dysfunction</td>
<td>Staphylococcal pneumonia</td>
<td>5</td>
<td>17</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>Persistent sputum infection</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>Herpes simplex pneumonitis</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

*Diagnosed by histological examination.
for age and carpal bone ages were three and four years, respectively, behind their chronological ages. Patient 1, whose height at the time of heart-lung transplantation was above the 50th centile, 15 months later has a height just above the 25th centile, probably the effect of repeated courses of prednisolone required to treat rejection episodes.

Discussion

After success in adults, cardiac transplantation is now an accepted treatment for children with end stage cardiac disease.\textsuperscript{15-17} Our early experience suggests that heart-lung transplantation is an acceptable procedure in children.

The number of children who may benefit from heart-lung transplantation may be assessed by examining the mortality statistics for the age group 5–15 in England and Wales. In 1986 the number of deaths for cystic fibrosis, Eisenmenger's syndrome, and primary pulmonary hypertension, were 40, 17, and three respectively. The number of patients represented with primary pulmonary hypertension may be an underestimate because, as our second case clearly illustrates, it may not be possible to diagnose it in life. This may also be true for Eisenmenger's syndrome where the diagnosis is frequently omitted from death certificates.

Patients are selected if they are considered to have a poor prognosis. In primary pulmonary hypertension, prognosis appears to be associated with low mixed venous oxygen saturation ($\text{ScVO}_2\%$). Fuster et al have shown that patients with an $\text{ScVO}_2\%$ below 63% have only a 17% chance of surviving untreated for three years, and those with an $\text{ScVO}_2\%$ of 63% or above have a 55% chance of surviving this period.\textsuperscript{18} Survival in untreated Eisenmenger's syndrome is more difficult to predict and we have been guided largely by the patient's symptoms. We are currently evaluating the minimum arterial oxygen saturation and distance walked in the 12 minutes as an indication of cardiorespiratory disability.\textsuperscript{5} In heart disease a raised pulmonary vascular resistance precludes heart transplantation,\textsuperscript{19} and for these patients heart-lung transplantation is a therapeutic option.

Hypoxic hypercapnic respiratory failure associated with right axis deviation on the electrocardiogram is an ominous sign in cystic fibrosis.\textsuperscript{19} The FEV$_1$, a further prognostic indicator,\textsuperscript{20} was below 30% of the predicted value in all of the patients with cystic fibrosis accepted onto our waiting list.\textsuperscript{3}

Contraindications to heart-lung transplantation include other organ dysfunction. This is particularly relevant in patients with cystic fibrosis. Evidence of liver disease makes surgery hazardous because of clotting abnormalities and has implications for long term survival. Such patients may be considered for combined heart, lung, and liver transplantation.\textsuperscript{21} Previous cardiothoracic surgery heightens the risk of bleeding postoperatively. Previous pleurectomy or pleurodesis are currently contraindications to surgery, but a previous thoracotomy for the correction of cardiac anomalies as in patient 4, or lobectomy, are not contraindications. High dose steroid treatment delays wound healing and we reduce treatment to the minimum dose possible while the patient is awaiting the transplant.

Infection and rejection are the major problems encountered in long term patient management. Monitoring of lung function allows early detection of infection and rejection,\textsuperscript{22} and the diagnosis is confirmed by transbronchial biopsy.\textsuperscript{12} Primary cytomegalovirus pneumonitis, which is a common cause of death in heart-lung transplantation, occurs when cytomegalovirus antibody negative recipients receive organs from donors who are antibody positive. A rapid test of cytomegalovirus antibody status became available in 1985 and has enabled us to ensure that cytomegalovirus negative recipients receive organs only from negative donors.\textsuperscript{23} Since this policy was adopted there have been no further deaths from organ transmitted cytomegalovirus disease.\textsuperscript{24}

In our series of 51 recipients of heart-lung transplants we have had five cases of herpes simplex pneumonitis. Herpes simplex pneumonitis has been previously reported in recipients of heart-lung transplants, but proved fatal.\textsuperscript{25} The prompt diagnosis by transbronchial biopsy and early treatment with acyclovir contributed to a successful outcome in patient 4.

The actuarial survival of 78% and 68% at one and two years respectively that we have reported for all heart-lung transplant recipients supports an optimistic outlook for transplantation in children.\textsuperscript{4} Major concerns in the paediatric age group relate to chronic rejection and the long term side effects of immunosuppression. We have shown that the development of obliterator bronchiolitis is related to previous inadequately treated episodes of rejection.\textsuperscript{26} Therefore adequate immunosuppression and early detection and treatment of rejection episodes should improve survival. There is a significant long term morbidity related to the use of both cyclosporin and corticosteroids. Morphological changes in the kidney after treatment with cyclosporin include interstitial fibrosis and glomerular sclerosis, which may be related to a cyclosporin induced reduction in renal blood flow and glomerular filtration rate.\textsuperscript{27} We use steroids routinely only for the treatment of rejection episodes and so would anticipate that steroid induced growth suppression will
be a problem only in that group of patients, of whom patient 1 is a typical example, who experience recurrent episodes of rejection.

Heart-lung transplantation is acceptable treatment for children with terminal respiratory disease. Although information on long term survival is not yet available, the improved quality of life in the short term in the children we have treated is encouraging.

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References

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Commentary

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The development of heart-lung transplantation as a new treatment for severe irreversible respiratory failure has given new hope to a large number of patients and their families facing the prospect of premature death. The extension of this procedure to the paediatric age range was inevitable and it is reassuring that the results that have been obtained from the first few cases are at least as good as those in adults. Any paediatrician who has the experience of seeing a child in terminal respiratory failure, miraculously given new life after a transplant, can only be immensely optimistic and positive about this procedure. However, it is most important that it should be put into perspective with a clear understanding of what is involved.

A practical treatment it may be for children in terminal respiratory failure. However, only a few individuals in this predicament will benefit from transplantation. From the Papworth experience so far, only 15% of referred patients have benefited.
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