EN BLOC HEART AND LUNG TRANSPLANTATION IN FINLAND 1988–1996

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ABSTRACT

The purpose of the study was to review the first clinical experience in combined heart-lung transplantation in our institution.

Material. From June 1988 to December 1996 15 en bloc heart and lung transplantations were performed. There were nine men and six women, aged 17–61 (mean 42.3) years. The indications for operation were primary pulmonary hypertension with right heart failure in five, Eisenmenger’s syndrome in five, pulmonary embolism and right heart failure in three and emphysema with right heart failure in two cases.

Results. The hospital (30 day) mortality was four patients (26.6 %). The causes of mortality were graft failure in two cases, infection and bleeding after transbronchial biopsy in one case and sepsis and aspergillosis in one case. Postoperative complications included eight cytomegalovirus (CMV), two Pneumocystis Carinii, five bacterial and five fungal (one Aspergillus and four Candida) infections. Rejection episodes (of the lungs) occurred in four patients (in 27 %).

During the follow-up to four years two patients developed diabetes mellitus (insulin therapy), one patient renal failure (dialysis), two patients tracheal stricture (laser resection), one patient fracture of the spine and one patient epilepsy. One patient died from prolonged CMV infection and chronic rejection eight months postoperatively.

Four patients underwent bronchial artery revascularization (two with the internal thoracic artery and two with a vein graft). This was followed by improved airway healing and resistance towards infections.

After a follow-up to four years 10 patients out of 15 (66.7 %) were living an active life.

Conclusion. Combined heart-lung transplantation offers a good mid-term outcome for patients with end-stage cardiopulmonary disease. The results compare favourably with the corresponding international statistics.

KEY WORDS: HEART-LUNG TRANSPLANTATION; CMV AFTER TRANSPLANTATION; BRONCHIAL REVASCULARIZATION

INTRODUCTION

Combined heart-lung transplantation in man was first attempted by Denton Cooley in 1968. The patient, a 2-month-old infant died, however, 14 hours postoperatively (1). In 1969 Walton C. Lillehei performed the second such operation on a 43-year-old patient with emphysema and pulmonary hypertension (2). The patient survived eight days. The third operation was performed in Cape Town by Christiaan Barnard in 1971. This patient did originally well but died afterwards 23 days later from bronchopleural fistula and infection (3). In 1981 Bruce Reitz at Stanford University Medical Center started the first successful clinical heart-lung transplantation programme after very thorough experimental work with rhesus monkeys. The availability of improved immunosuppression regimen, including cyclosporine, better postoperative care and control of infections resulted in the first long-term survival of the patients (4). The Stanford experience encouraged other transplantation centres to start their own activity on this field. The first human en bloc heart-lung transplantation was performed in Finland in June 1988. Since then 15 such operations have been performed. The experience obtained is reported below.
En bloc heart and lung transplantation

### TABLE 1

<table>
<thead>
<tr>
<th>Indications for operation</th>
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<tr>
<td>Eisenmenger’s syndrome</td>
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<td>Primary pulmonary hypertension</td>
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<td>Pulmonary embolism</td>
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<td>Pulmonary emphysema</td>
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<td><strong>All</strong></td>
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### TABLE 2

<table>
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<th>Causes of death</th>
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<tr>
<td>Graft failure due to pulmonary oedema</td>
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<tr>
<td>Infection and bleeding after TBB</td>
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<tr>
<td>Aspergillosis and sepsis</td>
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<tr>
<td>CMV and chronic rejection</td>
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CMV = cytomegalovirus
TBB = transbronchial biopsy

### MATERIAL AND METHODS

Between June 1988 and December 1996 15 en bloc heart-lung transplantations were performed in our institution. There were nine men and six women, age 17–61 (mean 42.3) years. The underlying diseases of the end-stage failure of the heart and lungs were Eisenmenger’s syndrome in five, primary pulmonary hypertension in five, pulmonary embolism in three and pulmonary emphysema in two cases (Table 1). The cause of brain death of the donors, aged 13–53 (mean 32.7) years was cerebral bleeding in seven cases, head injury in five cases and carotid dissection, brain tumour and cerebral infarction in one case each, respectively.

Distant procurement, modified Euro-Collins solution and prostaglandine E1 for the lungs and St. Thomas cardioplegia solution for the heart were used as preservatives. Anastomosis of the trachea 1–2 cm above the bifurcation with 3-0 Prolene® or PDS®, anastomosis of the right atrium with 3-0 Prolene and aorta with 4-0 Prolene were performed in this order. Details of the operative procedure technique of Bruce Reitz (4, 5) were followed with the exception of bronchial revascularization in four cases. This was done with a vein graft in two cases and with the internal thoracic artery in two cases. For this purpose a cuff of descending aorta with the origin of the bronchial arteries was preserved. On this cuff a vein or the internal thoracic artery was anastomosed end to side.

In selection of the donors ABO blood groups, patient size and later cytomegalovirus matching were used.

The immunosuppression consisted of antithymocyte globulin (Fresenius or Merieux, 2.5 mg/kg) for five postoperative days, cyclosporine A, starting on the first or second postoperative day (250–350 μg/L trough level), azathioprine 2 mg/kg (WBC > 3000/ml) and methylprednisolone starting with 1 g daily for three days and tapering it down to 4–12 mg per day during the hospital stay. Rejection episodes were treated with prednisolone 1 g daily for 3 days. In two patients additional OKT-3 was needed.

Prophylactic acyclovir 800 mg a day was given to all patients for six weeks and prophylactic gancyclovir for six weeks to one CMV negative patient with a graft from a CMV positive donor.

### RESULTS

#### MORTALITY

The hospital (30 day) mortality was four patients (26.6 %). Eleven out of 15 patients (73.4 %) were survivors after the primary hospitalization period. There was one later death at eight months postoperatively yielding 10 long-term survivors (66.7 %). The actuarial survival is presented in Fig 1.

The causes of mortality are listed in Table 2. There were 2 acute graft failures from pulmonary oedema. The other three causes were: 1) acute respiratory infection associated with bleeding after transbronchial biopsy, 2) aspergillosis and sepsis and 3) cytomegalovirus infection associated with chronic rejection.
REJECTIONS
Rejection episodes occurred in four patients, in one of them three times. None of these were fatal. In two patients the rejection did not subside with steroids alone. Both of them responded favourably to OKT-3.

INFECTIONS
Infections were the most common complications (Table 3). Eight patients had cytomegalovirus infection. One of these was fatal. It occurred in a CMV negative recipient who received a graft from a CMV positive donor. Prophylactic gancyclovir treatment could not prevent the development of the infection which was finally associated with bronchiolitis obliterans and demise of the patient. Major febrile bacterial infections occurred in five patients. One of them was associated with aspergillosis of the transplanted lungs and death of the patient. In four patients who developed oral candida and in one patient with an oesophageal candida infection resulted in cure with oral ketoconazole treatment.
Infection of the tracheal anastomosis resulted in excessive granulation tissue and later stricture formation in two patients. These were treated by endoscopic resection with Laser beam. At re-examination three months later a complete cure of the lesion was observed in both cases.

BRONCHIAL ARTERY REVASCULARIZATION
Patients with bronchial revascularization had a better blood flow of the bronchial mucosa at Laser Doppler endoscopic flow measurement and faster immediate recovery after the transplantation.

OTHER COMPLICATIONS
One patient developed postoperative renal failure which necessitated haemodialysis for
five weeks postoperatively. At microscopy of a fine needle renal biopsy cyclosporine induced vascular damage was suspected. Two patients had postoperative bleeding which required reoperation.

One patient developed epileptic seizure three months postoperatively. Computed tomography of the brain was normal. When the patient had another seizure antiepileptic treatment was started. He has remained asymptomatic since then.

One patient later developed a compression fracture of the 12th vertebra. He was 61 years old (the eldest in the series) and had generalized osteoporosis. Despite of Miacalcic treatment and other therapeutic measures the rehabilitation of the patient was unsatisfactory and he has needed rollator support when walking outside.

In two patients diabetes mellitus was diagnosed during the follow-up. Both were later put on an insulin regimen.

DISCUSSION

Ten (10) out of 15 patients with combined heart-lung transplantation (i.e. 66.7%) were alive after a follow-up to four years with an average follow-up of two years. This result compares favourably with the international statistics (6). The operation has become a well established procedure to treat patients with end-stage cardiopulmonary disease. Because of limited number of donors, only those patients with irreversible pulmonary damage and right heart failure, which is not expected to subside after pulmonary transplantation, are accepted for combined transplantation of the heart and lungs. The centres performing heart-lung transplantation are not as many as centres performing only cardiac transplantations. This may be due to the fact that more complications are expected to occur after en bloc heart-lung transplantation. The procedure is inevitably associated with interruption of the nervous, lymphatic and bronchial circulatory blood supply to the lungs as well as total denervation of the heart. Denervation of the lungs results in disappearance of the Hering-Breuer and cough reflex. This in turn leads to impaired drainage of the bronchial secretions and increased risk of infections.

The transplanted lungs contain lymphoid and reticuloendothelial tissue with plenty of major histocompatibility antigens. These antigens can give rise to increased risk of rejection (7).

Therefore, the risk of both infection and rejection is much higher after combined heart and lung transplantation than after heart transplantation alone. Also, rejection involves the lungs more often than the heart in combined procedures (8, 9).

Infections played a major role in both morbidity and mortality in the present series. Infection was involved in the demise of three patients. One of them had a septic bacterial infection combined with aspergillosis of the lungs. The other had chronic CMV infection and chronic rejection (bronchiolitis obliterans). The third one had an acute respiratory infection. In order to rule out rejection, endobronchial biopsy was taken. This resulted in bleeding which, together with infection, led to the demise of the patient.

Cytomegalovirus was the most frequent cause of infective complications: eight patients out of 15 had clinically symptomatic CMV infection. The patient with the fatal outcome was CMV negative preoperatively and received a graft from a CMV positive donor. The prophylactic gancyclovir therapy postoperatively could not save him from the clinical infection and fatal outcome.

This patient developed also bronchiolitis obliterans. Because of this experience and the accumulating data from the literature we stopped using a graft from a CMV positive donor to a CMV negative lung recipient. The role of CMV in the pathogenesis of bronchiolitis obliterans is still under debate (10, 11). In recent reports from Stanford University no correlation between cytomegalovirus infection and bronchiolitis obliterans could be established (10).

Rejection episodes occurred in only four out of 15 patients (27%). This did not differ from the rejection incidence of our cardiac transplant patients. All of the rejections involved only lungs. The diagnosis of rejection was based on clinical signs, fall in expiratory flow, chest X-ray, high resolution computed tomography and endobronchial biopsy. Most of the rejections responded favourably to the steroid treatment. In two cases only, administration of OKT-3 was necessary. During the treatment of rejection the patients also received prophylactic antibiotics. It was felt that the risk of infections was increased during the increased immunosuppression.

As a side-effect of prolonged steroid ther-
apy, compression fracture of the spine occurred in one patient. In order to avoid systemic side-effects of the corticosteroids, two of our patients are now on inhaled steroids. Their condition is stable so far. On the basis of this limited experience we do not know yet whether this mode of therapy is more advantageous than peroral treatment in the long run.

In four cases bronchial artery revascularization was performed. This procedure seemed to result in improved postoperative recovery and reduced infections. The time span is too short so far to tell anything about the long-term effects of the procedure on the development of bronchiolitis obliterans, infections and lung function (12,13,14).

All except one of the surviving patients are living very active lives. The patient with spinal fracture still needs support when walking. Two of the female transplant patients have successfully participated in sports events e.g. in Annual European Transplant Games.

It can be concluded that combined transplantation of the heart and lungs carries higher risks of infections and other complications compared to heart transplantation alone. The patients need intensive observation and vigorous diagnostic and therapeutic measures to prevent and treat the complications. The procedure can, however, offer an opportunity for active life in a patient with end-stage cardiopulmonary disease when other therapeutic measures are unable to save life.

REFERENCES


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