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Early graft function following heart and lung transplantation

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Abstract. Fifty-one patients underwent heart-lung transplantation between April 1984 and October 1988. The first five donor organs were removed in an adjacent operating theatre. Organs were subsequently removed from distant centres. The method of preservation consisted of cold cardioplegic arrest of the heart using St. Thomas' solution, followed by a simple, cold pulmonary artery flush of a lung perfusate developed at Papworth Hospital. Administration of the solution was preceded by an infusion of prostacyclin into the pulmonary artery during preliminary dissection of the donor organs. The total ischaemic time ranged from 48 to 51 min (mean 49.6 min) for the near procurement group and from 70 to 249 min (mean 154.2 min) for the distant procurement group. There were no primary organ failures. Function of the lungs was assessed by gas exchange, pulmonary function tests, time to extubation, and survival data. Serial radiological studies were used to monitor graft performance in the postoperative period. We report here on our clinical experience of early graft function following heart and lung transplantation.

Key words: Heart-lung transplantation - Heart-lung, early graft function - Heart preservation - Lung preservation.

Combined transplantation of the heart and lungs, first successfully accomplished by Reitz and associates [12] in 1981, has become a successful therapy for many patients with end-stage cardiopulmonary disease. However, a lack of suitable donors and distant organ procurement techniques have restricted the growth of clinical heart-lung transplantation. Static hypothermia can provide short-term preservation of heart and lungs, though lung injury prevails with extended ischaemic periods [8]. The autoperfused, working heart-lung preparation [7] has been used successfully for distant organ procurement [5, 7, 10]; yet, it is not without its significant technical failures. Core cooling on cardiopulmonary bypass (CPB) has also been successfully used.

A Papworth perfusate has been developed, essentially extracellular in its constitution, which has been incorporated in a technique of preservation based on a single pulmonary artery flush previously described by this unit [6]. We have extended ischaemic times to over 4 h now and early graft function has been satisfactory.

Patients and methods

Between April 1984 and October 1988, a total of 51 heart-lung transplants were performed. There were three major recipient groups: (1) patients with primary lung disease, with or without a secondary cardiac disease; (2) patients with primary cardiac pathology and associated with pulmonary hypertension (Eisenmenger's syndrome); and (3) patients with pulmonary vascular disease (Table 1).

Table 1. Diagnoses of recipients of heart-lung transplants

Diagnosis	*n*
Eisenmenger's syndrome	14
Cystic fibrosis	12
Primary pulmonary hypertension (PPH)	8
Thromboembolic pulmonary hypertension	3
Sarcoidosis	3
Emphysema	4
Primary biliary cirrhosis and PPH	1
Fibrosing alveolitis	2
Histiocytosis X	2
Bronchiectasis	1
Pulmonary artery leiomyosarcoma and pulmonary hypertension	1

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Table 2. Causes of death in donors

	n
Head injury	25
Intracranial bleed	23
Brain tumour	2
Other	1

There were 24 male and 27 female recipients. The mean age for the group was 28.5 years (SD 9.6 years) and the range 11-52 years. One of the patients had previously had a sternotomy performed, and in five a thoracotomy had previously been performed.

Donor selection

The criteria for selection of suitable donors for heart and lung transplantation have already been outlined by this group [4]. There were 30 male and 21 female donors with a mean age of 26.0 years and a range of 8-45 years. The causes of death are outlined in Table 2.

The first five donors were transferred to Papworth Hospital whilst organs from 46 additional donors were being procured from various centres within the United Kingdom.

Mean donor ventilation time was 37 h (SD 25 h; range 6-144 h). Matching was for ABO compatibility. A direct cross-match for cytolytic antibodies was not done unless testing against a random sample of lymphocytes showed cytolytic antibodies. Organs from donors with positive cytomegalovirus serology were transplanted only into seropositive recipients.

Attempts were also made to place donor lungs in suitably sized recipients, since donor lungs that are too large can cause atalectasis and impairment of gas exchange. We used chest x-ray measurements of the height of the thoracic vertebral column and of the width of the rib cage of both the donors and the recipients [4]. Difficulties are sometimes experienced in obtaining accurate x-ray measurements from distant hospitals, resulting in difficulties in size matching. Measurement of total lung capacity (TLC) pre-transplant provides a means of determining the lung size that best matches a recipient's chest cavity, and this provides an alternative method of donor selection. In the absence of chest disease, the TLC of the donor may be safely predicted on the basis of age, sex, and height [3]. An appropriate recipient may then be selected whose measured TLC either matches or is marginally larger than this (+1000 ml for adults). This method, which was employed in our 51 heart-lung recipients, offers simplicity of operation and avoids the errors that may arise from measurements of vertical heights and transthoracic diameters on the chest radiograph, especially in the distant procurement of grafts.

Methods

All of the heart-lung transplants were carried out between April 1984 and October 1988. Details of the operative technique for harvest and implantation have been described previously [6].

Assessment of function

Assessment of postoperative graft function relied upon serial blood gas analysis, serial radiological survey, and routine pulmonary function tests to clinically follow immediate and early graft function. Assessment of alveolar-arterial oxygen gradients ($A\text{-}aO_2$), using a modified form of the alveolar gas equation [3, 16] was also undertaken.

Results

The total time for which the donor organs were ischaemic varied from 48 to 51 min (mean 49.6 min) for the near procurement group and from 70 to 249 min (mean 154.2 min, SD 37.3 min) for the distant procurement group (Fig. 1).

All heart-lung blocs harvested were implanted with no primary organ failures. Immediate graft function was satisfactory in all 51 patients. These patients were weaned from CPB with a mean inspired oxygen tension (FIO_2) of 49.7% (range 28%-60%).

The mean time to extubation of the group was 26.2 h (range 4-58 h), whilst 43 of these patients were extubated within 48 h. These patients were well enough to maintain a normal arterial PO_2 without the use of an oxygen mask by the end of the 1st week. One patient early in the experience was extubated within 24 h but was reoperated upon on the 7th post-operative day for a tracheal dihiscence; the patient eventually died. One patient received lungs that were thought, in retrospect, to be oversized for the recipient; she died of a complication of a perioperative cerebrovascular accident on day 12. Another patient

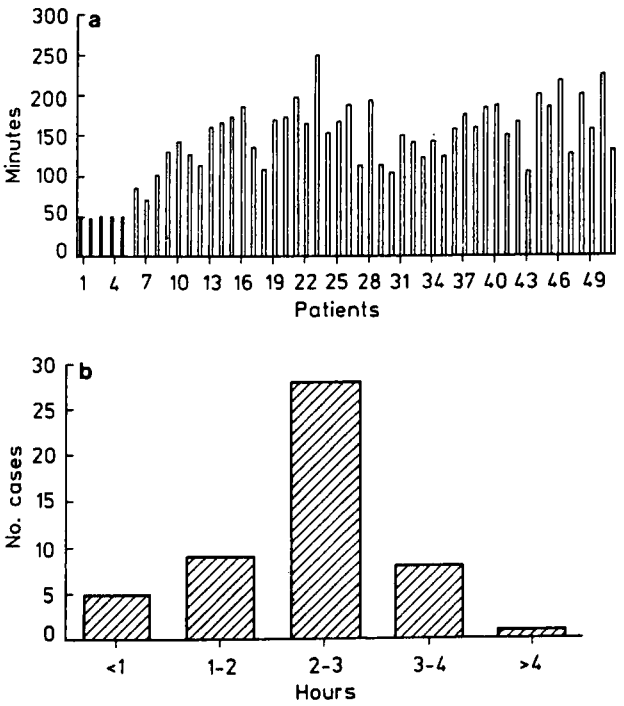

Fig. 1. **a** Total ischaemic times for overall group. ■, Local procurement, □, distant procurement; **b** ischaemic time distribution

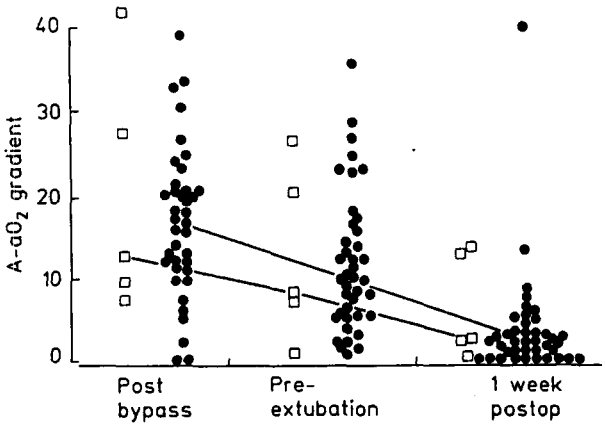

Fig. 2. Alveolar-arterial oxygen gradient *(A-aO$_2$)* in kilopascals for near and distant procurement groups at various times postoperatively. *Lines* show median response at each period. □, Local procurement; ●, distant procurement

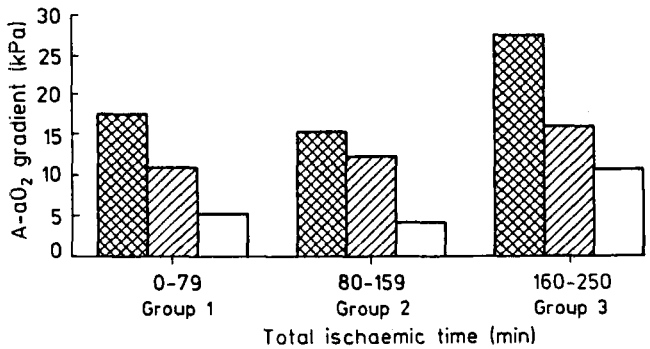

Fig. 3. Effect of total ischaemic time on mean alveolar-arterial oxygen gradients *(A-aO$_2$)*. ⊠, After cardiopulmonary bypass; ⊡, preextubation; □, 1 week postoperatively. Mean time to extubation in group 1 = 24 h, in group 2 = 27 h, in group 3 = 21 h

developed an empyema in the chest and died from staphylococcal septicaemia on day 29. Re-exploration for continuing haemorrhage was required in nine cases; four of them had Eisenmenger's syndrome, two had undergone a previous thoracotomy, and all had preoperative pulmonary hypertension. As a result of the need for repeated CPB, one patient with severe liver disease developed adult respiratory distress syndrome and died. No long-term complications resulted from re-exploration. Cardiac graft function was intially poor in one case, and this was probably due to subendocardial infarction prior to extraction of donor organs.

The alveolar-arterial oxygen gradients were serially measured just after discontinuation of CPB, prior to extubation, at 8 h, at 24 h, and at appropriate intervals in the 1st postoperative week (Fig. 2). These values, higher initially, fell significantly with improving graft performance. The median A-aO$_2$ gradients for the three time points shown (FIO$_2$ values were most reliable on ventilators and air, whereas face masks have a variable delivery and depend on patient compliance) for the near procurement group were: 12.8 kPa, 8.3 kPa, and 2.5 kPa, respectively. Gradients of 16.9 kPa, 9.8 kPa, and 2.3 kPa, respectively, were obtained in the distant procurement group.

Comparison of the near and distant procurement groups at these measured points using the nonparametric Wilcoxon test showed no significant difference; preservation was effective in both groups. Both groups showed a significant fall of A-aO$_2$ gradients between each time point ($P < 0.005$ nonparametric Friedman test).

With reference to A-aO$_2$ gradients and extubation data, increasing ischaemic time did show a trend in diminishing early graft performance, but this was not significant (Fig. 3).

Heart-lung transplantation was performed in 51 patients. Thirty-seven of them are alive between 1 and 54 months after surgery. Actuarial probability of survival was calculated at 76% at 1 year, 68% at 2 years, and 58.5% at 3 years (Fig. 4). All but three surviving patients now enjoy an unrestricted lifestyle, and most have returned to their previous occupations. One patient is undergoing advanced combat training in the army, and another earned a gold medal at the World Transplant Games.

There have been 14 deaths in the group, four of which occurred within 30 days of transplantation. One patient died of liver failure at 11 days, one young girl developed a massive cerebrovascular accident and died at 12 days, another patient died of a ruptured aorta at day 22 following infection in the mediastinum, whilst a fourth died of overwhelming infection on day 29. One of the deaths in the first five patients was in a patient who was on steroids and who died at day 39 as a result of a tracheal dehiscence. There were four deaths from cytomegalovirus

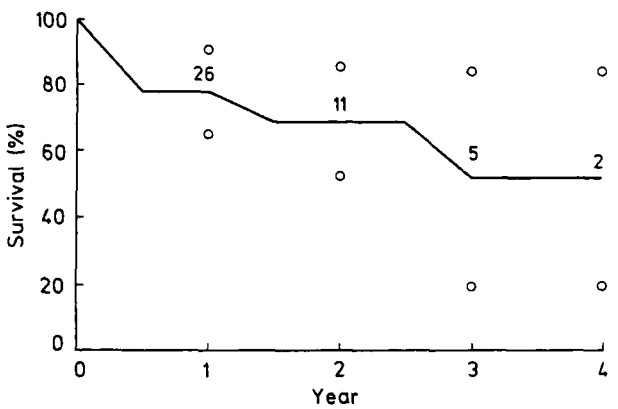

Fig. 4. Actuarial survival curve for heart-lung transplantation at Papworth Hospital

infection at days 44, 46, 85, and 145. There were two deaths as a consequence of obliterative bronchiolitis on days 410 and 416. One patient, who underwent left single lung transplantation for obliterative bronchiolitis in his heart-lung transplant, died 19 days after his second operation after suffering a massive small bowel infarction consequent to his systemic lupus erythematosis.

Eighty-five percent of all recipients had normal forced expiratory volume in 1 s (FEV1) and forced vital capacity (FVC) at 6 months. Both patients surviving beyond 4 years have normal lung function.

Discussion

It was widely believed that the achievement of safe and reliable distant graft procurement in heart-lung transplantation would increase the numbers of transplants performed, as it did in cardiac transplantation [2]. Despite extensive experimental and clinical investigations [8, 14], there remains no consensus on the optimal technique for distant lung procurement. If combined heart-lung transplantation is to achieve its potential in serving the largest number of patients, such a technique needs to be safe, flexible, reproducible, and accepted by the transplant community.

In this institute we have used a technique that is fully compatible with the requirements of other multiorgan donor teams. Technical complexity with the autoperfusing heart-lung preparation has resulted in primary organ failures and liver wastage [7]. Whilst core cooling has been used successfully, it is acknowledged that we still do not fully understand the effect of bypass on other organ function.

The trend towards longer ischaemic times, as shown in Fig. 1, reflects our increasing confidence in this method. The ischaemic times within our experience would allow distant harvest anywhere in the British Isles or in most centres in Western Europe. Whilst impairment of lung function tends to increase with longer ischaemic times, in our experience this has not been significant. Virtually any method of lung preservation must extend the tolerated ischaemic time beyond 4 h.

Pulmonary oedema is one of the most consistent sequelae of prolonged ischaemia [11, 13, 15], though serial measurements of total and extravascular lung water are not clinically applicable. No correlation between lung cell viability and functional or morphological findings is found in increasing ischaemic lung times [1, 9]. Moreover, the histopathological findings within a preserved lung are quite heterogenous, normal lung juxtaposed with areas of severe reperfusion injury, thereby eliminating the use of lung morphology to qualify a preservation technique [8].

Radiological surveillance is of value in assessing the lung's postoperative performance. While interstitial or alveolar shadowing can indicate pulmonary oedema, no grading has been reported of the radiological evidence of ischaemic injury to the lung, and it is unlikely that radiological findings could be more specific or sensitive than histopathology. We have not experienced a "reimplantation response" in this series though serial radiology remains the mainstay of our clinical surveillance.

The radiograph was abnormal in 74% of the biopsy-proven episodes of rejection in the 1st postoperative month. Changes were often associated with pleural effusions. They consisted of ill-defined bilateral and lower zone nodules, which sometimes cholest to produce areas of consolidation. They were not specific and were also seen with CMV pneumonitis. Staphylococcal pneumonia during the early postoperative period caused the more distinctive appearance with lobar consolidation and abscess formation.

Whilst the radiographic appearances in this 1st postoperative month did not permit a distinction to be made between rejection and infection, they offered a useful indication along with pulmonary function tests for transbronchial biopsy and bronchial lavage. Transbronchial biopsy improved the accuracy of diagnosis of acute lung rejection and allowed a distinction to be made between rejection and infection. After the 1st month, the chest radiograph is frequently normal during episodes of acute rejection (only 23% of the episodes were associated with radiographic abnormalities), emphasising that a normal chest radiograph does not exclude acute rejection.

The limited data available suggest that pulmonary haemodynamics are affected by preservation, though these changes do not necessarily reflect the degree of ischaemic damage [8, 17].

In the clinical setting of this program, we have closely followed serial arterial gas analysis, clinical observation, and serial x-rays to monitor performance. Immediate weaning from CPB and extubation is related to the quality of preservation. Falling $A\text{-}aO_2$ gradients in this series have reflected the increasing performance for both short and longer ischaemic times. Survival data and laboratory respiratory function tests have enabled us to monitor the continued graft performance and to testify to a markedly improved quality of life.

It remains to be seen how successful our attempts will be to extend the ischaemic period, but it is only in so doing that we can expand the availability of heart-lung transplantation.

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