PAPERS AND ORIGINALS

Recent experience with heart transplantation

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Summary and conclusions

The major factors contributing to the recommencement of clinical heart transplantation in the United Kingdom last year were the steadily improving results from Stanford University, the clarification of the diagnosis of brain death, and advances in preserving donor hearts. Twelve men aged 16 to 52 years received heart transplants at Papworth Hospital from January 1979 to July 1980. Six had cardiomyopathies and six ischaemic heart disease. The donors were aged 16 to 35 (mean 21) years. A combination of road and air transport was used to transport the heart to Papworth in seven cases. The total donor heart ischaemic time ranged from 108 to 171 minutes (mean 151), and early graft function was satisfactory in all cases. Postoperative management was directed towards preventing rejection and infection. Equine antihuman thymocyte globulin, prednisolone, and azathioprine were used for immunosuppression. Endomyocardial biopsy was performed every 10 to 14 days during the early postoperative period. There were three deaths: one at 17 days from brain damage and two at 59 and 76 days from rejection. Of the remaining nine patients six left hospital and three returned to work.

The number of patients who might benefit from heart transplantation is large, but the cost is high. The cost would fall if an effective non-toxic immunosuppressive agent were developed. Meanwhile, a careful evaluation of the benefits of heart transplantation should continue.

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Introduction and historical background

It is now more than 12 years since Christiaan Barnard performed the first human heart transplant.[1] The patient lived only 18 days before dying from a combination of infection and rejection. A month later a second operation was performed, and the recipient, a 58-year-old dentist, lived nearly two years before dying from chronic rejection of the transplanted heart.

These operations heralded a wave of misplaced enthusiasm, and during 1968 and 1969 about 150 transplants were performed by more than 60 teams in all parts of the world. Many surgical teams had their reputations tarnished by embarking on heart transplantation without a proper understanding of the complex issues involved. At the same time, the publicity given to some of the personalities and events surrounding the operations had an adverse effect on many members of the public and medical profession. A combination of this and the generally low survival rates resulted in the work being abandoned in all but a few centres, so that by the beginning of 1978 there were only five places in the world where heart transplantation was still being practised.

Against this background, a question often asked during the last year has been: "Why should heart transplantation have started again in Britain at this particular time?" Three factors have been of most importance. Firstly, Stanford Medical Centre has produced convincing evidence that heart transplantation can be an effective form of treatment for patients dying from terminal heart disease. Secondly, there has recently been an important change in professional and public attitudes towards the concept of brain death, which has greatly facilitated the process of heart donation. And, thirdly, there have been important advances in preserving the functional integrity of donor hearts between their excision and their reimplantation, thereby allowing us to conceive of a much wider potential supply of donor organs than had previously been possible.

RESULTS FROM STANFORD

Dr Norman Shumway started an experimental programme in heart transplantation at Stanford University in California in the middle 1950s. Most of the important early work on technical aspects of the operation, preservation of organ function, and detection of rejection came from his laboratory.[2-4] An active clinical programme started at the beginning of 1968, and during

the ensuing decade the expectation of survival after operation steadily improved.[5] Graft survival became comparable with that achieved in cadaveric kidney transplantation[6] and survival rates after operation improved to 66% at one year and 58% after three years.[7] Perhaps more important than crude survival statistics was the demonstration that the great majority of patients surviving the first year enjoyed useful and active lives.[8] These are the results that we ought to be able to achieve now, provided the same degree of care and attention to detail is brought to all aspects of the work as has been the case at Stanford.

CONCEPT OF BRAIN DEATH

In October 1976 the Conference of Medical Royal Colleges and their Faculties in the United Kingdom published a unanimous report clearly defining the clinical criteria for the diagnosis of brain death.[9] The main impetus for the report arose from the consequences of the development of intensive care techniques, whereby the vital functions of respiration and heart beat could be maintained artificially after the brain had been irreversibly damaged, thereby posing difficult problems about when this artificial support should be withdrawn. Inevitably, however, the report had important implications for procuring donor organs for transplantation, and the Chief Medical Officer of Health alluded to this in a letter to all hospital doctors dated 9 January 1978, in which he wrote: "The conclusion that respiration and a beating heart are being maintained solely by mechanical means and that brain death has occurred is reached entirely independently of any transplant considerations. However, once the diagnosis of death has been made the actual moment at which a respirator is switched off may be influenced by the need to maintain the kidneys or other organs in the best possible condition before they are removed for an eventual transplant."

These issues were further clarified in 1979 in another memorandum from the Conference of Medical Royal Colleges: "It is the conclusion of the conference that the identification of brain death means that the patient is dead, whether or not the function of some organs, such as heart beat, is still maintained by artificial means."[10]

DONOR HEART PRESERVATION

These reports and the general acceptance of their conclusions by the medical profession set the scene for greater availability of suitable donor hearts. Nevertheless, as recently as three years ago Shumway declared that he considered it unethical to perform clinical heart transplantation unless the donor and recipient operations were conducted in adjoining theatre suites, so that donor heart ischaemic times could be kept to an absolute minimum. There remained, therefore, the need to develop preservation techniques whereby donor hearts could be safely stored for long enough so that all potential donor organs offered within the United Kingdom could be used. Only in this way did it seem feasible to obtain enough suitable donor hearts to sustain an active clinical programme.

Preliminary experiments with pigs on cardiopulmonary bypass suggested that the heart could be satisfactorily preserved using single-dose cold cardioplegia and rapid induction of local profound cardiac hypothermia for up to four hours' ischaemia. Thereafter morbidity from prolonged cardiopulmonary bypass became a limiting factor. We therefore tested the same preservation techniques using orthotopic transplantation in pigs after 16 hours' ischaemia as the experimental model and showed good graft function in most of these experiments.[11] This suggested that clinically it would be reasonable to use identical techniques for storage times of up to at least six hours and that by using a combination of road and air transport it should then be possible to accept donor organs from almost any hospital in Britain.

Methods

We began to prepare for a programme of heart transplantation at Papworth Hospital about six years ago. Throughout this period we were guided by the belief that if we based our methods on Stanford practice we might be able to achieve a similar degree of success.

RECIPIENT SELECTION

The selection of patients for transplantation has been the dual responsibility of cardiologist and cardiac surgeon. After careful screening of the relevant medical data and recent cardiac investigations, prospective recipients are admitted to hospital for three to five days for definitive assessment. All potential recipients should have advanced heart disease unresponsive to further medical or conventional surgical treatment and have a poor prognosis for surviving the next six to 12 months. They should be psychologically stable and strongly motivated to accept the chance of an extension of their life expectancy and preferably come from a stable social background.

Early experience at Stanford showed that older patients tolerated the procedure less well, and we have felt disinclined to offer transplantation to children. We therefore set age limits of 15 and 50 years. Other contraindications include a raised pulmonary vascular resistance above 10 Wood units, active infection, and insulin-dependent diabetes mellitus. Recent pulmonary infarction is a relative contraindication, as is advanced cardiac cachexia. There should be ABO blood group compatibility between recipient and donor and a negative lymphocyte cross-match between recipient serum and donor cells. Tissue typing is performed on all recipients and donors, but we do not at present regard HLA mismatching as a contraindication.

SELECTION OF DONORS

Most donors have suffered irreversible brain damage as a result of road traffic accidents or intracranial haemorrhage and are receiving respiratory support by means of a ventilator. The diagnosis of brain death is made according to the defined criteria[9] by doctors entirely independent of the transplant team. Consent for heart donation must be freely given by the next-of-kin after a sympathetic explanation of what this means, and permission for the removal of named organs is obtained from the local coroner.

Because of the prevalence of undetected coronary artery disease in the general population, we are unwilling to accept hearts from men older than 35 or women older than 40 years. Whenever possible a medical history is obtained from relatives or the general practitioner and the cardiovascular system is always carefully examined, including examination of a recent electrocardiogram and a chest radiograph.[12] If hypotension is present when brain death is diagnosed, or develops subsequently, this is corrected with fluid replacement and, if necessary, inotropic support.

DONOR AND RECIPIENT OPERATIONS

The donor operation is timed to start in accordance with the necessary preparation of the recipient after his admission to hospital. The donor team, comprising surgeon, theatre nurse, and technician, then proceed to the hospital, where the final evaluation of the donor is made. Thereafter the donor and recipient teams maintain close communication by telephone.

If consent for kidney donation has also been granted their vascular pedicles are first exposed and then the donor heart is excised during venous inflow occlusion after the aorta has been clamped and the aortic root perfused with 1 litre of cold cardioplegic solution. The heart is then cooled rapidly by serial passage through bowls of cold saline and stored in a sterile plastic bag containing cold cardioplegic solution at 2-4°C, which in turn is placed in a Coolbox. Usually only at this stage is the instruction to start the recipient operation given.

The technique of orthotopic transplantation of the heart has changed little since its original description by Lower and Shumway in 1961.[13] After starting cardiopulmonary bypass, the recipient's heart is removed, leaving the posterior walls of the left and right atria with their venous connections. The donor atria are opened and then sutured to the corresponding structures in the recipient and the great vessels anastomosed last. Early postoperative management of the cardiovascular system is similar to that for patients undergoing routine cardiac surgery. Because of denervation of the donor heart a weak

isoprenaline solution is sometimes necessary for its chronotropic effect and any tendency to hypertension is treated with sodium nitroprusside. The rhythm may be nodal initially but usually a stable atrial rhythm soon develops.

POSTOPERATIVE MANAGEMENT

The most important postoperative complications are rejection and infection, and management protocols are directed towards the prevention and early detection of these two problems.

During the first few weeks after operation the patient is nursed in as sterile an environment as possible. Reverse barrier nursing is observed and visiting is limited. Nevertheless, a programme of daily exercises within the isolation cubicle is started as soon as possible. After completing the primary course of antithymocyte globulin, the patient is transferred to a single room fitted with an electrostatic clean air unit. Thereafter masks are worn only by those entering the room and by the patient when he is in the rest of the hospital. Rehabilitation is continued with daily sessions in the physiotherapy gym, and the patient is taught how to take his own drugs and instructed in their potential side effects. A close surveillance is kept for any signs of infection, which usually start in the respiratory tract. Daily chest radiographs are taken and any new radiographic opacities investigated immediately.

Immunosuppression starts before operation with loading doses of azathioprine and intravenous methylprednisolone and antithymocyte globulin. After operation oral prednisolone is started at 1 mg/kg body weight, reducing to 0·5 mg/kg by one month and 0·3 mg/kg by three months. Azathioprine is administered at a dose of up to 2·5 mg/kg with the purpose of keeping the white cell count in the region of 5×10^9/l. Equine antithymocyte globulin (Upjohn) is given by daily intravenous injection for the first three or four weeks and is regarded as an important part of the primary immunosuppressive regimen. The dose is adjusted to suppress the T-cell fraction of the circulating lymphocytes to about 5% of their preoperative value or to less than $0{\cdot}05 \times 10^9$/l. This is usually in the range of 10-15 mg/kg body weight.

Rejection episodes are most frequent during the first three months after transplantation, when the average incidence is 1 per 22 patient-days.[14] Thereafter they become much less frequent, declining to one episode per 325 patient-days after the first year. Clinical evidence of graft rejection, which includes fluid retention, a diastolic gallop rhythm, and signs of a low cardiac output are late phenomena and we make every effort to detect rejection before it has progressed this far. Of most help in this regard are changes in the daily electrocardiogram and endomyocardial biopsy. A drop of the summated QRS voltages in leads I, II, III, V1, and V6 of more than 20% suggests impending rejection and is an indication for cardiac biopsy, which is otherwise undertaken at intervals of about 10 days.

The treatment of rejection episodes depends on their timing and severity. If rejection occurs during the period of primary treatment with antithymocyte globulin, which is uncommon, it is treated with three or four daily doses of 1 g methylprednisolone. If it occurs later and is mild it is treated by reinstituting a short course of antithymocyte globulin; if it is moderate or severe high-dose pulses of methylprednisolone are added. Rejection episodes occurring after the patient has left hospital may, if mild, be treated by doubling the oral daily dose of prednisolone and then tapering the dose back to maintenance levels over the next two weeks. If the rejection process is graded histologically as more than mild, or if ECG voltages do not recover promptly the patient is admitted for treatment with intravenous antithymocyte globulin and methylprednisolone.

Patients are maintained on a low-cholesterol, low-sodium diet and encouraged to exercise daily. After leaving hospital they are seen in the outpatient clinic twice a week for a month, weekly for two months, and then about once a month. Continuing potential complications in the years after transplantation include infection,[15] accelerated coronary atherosclerosis in the transplanted heart,[16] and malignant neoplasms, usually of the lymphomatous type.[17] Complications arising from long-term steroid therapy are also important. Every year patients are admitted to hospital for a complete review, which includes coronary arteriography, left ventriculography, and cardiac biopsy.

Results

Twelve patients received heart transplants at Papworth Hospital from January 1979 to July 1980. Their ages ranged from 16 to 52 (mean 35) years and all were men. Six patients had cardiomyopathies and six ischaemic heart disease. During this period 164 patients were referred for consideration of transplantation, 54 of whom were admitted to hospital for further evaluation. Twenty-three patients were accepted for transplantation and six died while awaiting operation.

The ages of the donors ranged from 16 to 35 (mean 21) years. Three were women and nine men. Donor hearts were brought to Papworth by road in five cases and by a combination of road and air transport in seven cases. The total donor heart ischaemic time varied from 108 to 171 minutes (mean 151 minutes). Early function of the transplanted heart was excellent in all cases. The donor heart spontaneously defibrillated within two minutes of our releasing the aortic clamp on six occasions. Postoperative cardiac output was measured by an electromagnetic flow probe placed around the aorta in eight of the 11 cases and the mean measured cardiac output before closing the chest was 8·3 l/min.

At the end of July 1980 nine of the 12 patients were alive. The first patient operated on died 17 days after transplantation as a result of brain damage secondary to low cardiac output between induction of anaesthesia and the institution of cardiopulmonary bypass. A 36-year-old man died soon after leaving hospital 11 weeks after transplantation from undetected acute rejection of rapid onset, and another 47-year-old man died from rejection 59 days after transplantation. Of the remaining nine patients six had left hospital and three had returned to work. Of the three patients still in hospital, two were progressing satisfactorily, but the other had developed fits and impaired consciousness one week after transplantation and remained gravely ill.

Discussion

This report presents some of the factors that led us to restart heart transplantation in Britain. Our early experience is as yet too limited to know how successful this will be. Initial graft function has been excellent in all cases and it has been gratifying to see how critically ill patients can be transformed, sometimes within a matter of days, by restoration of a normal cardiac output. Most postoperative complications have been related to rejection episodes but these have usually responded to treatment with a short course of intravenous antithymocyte globulin and methylprednisolone. Major infectious complications have been relatively uncommon, although this remains one of the most important hazards to the surviving transplant patient.

The number of potential recipients is difficult to estimate and is clearly influenced by the strictness of the criteria for selecting recipients. This, in turn, would be affected by improved methods of immunosuppression, allowing a more predictable survival after transplantation. Even if one assumes that only 1 in 50 patients younger than 50 years dying from cardiac disease might be suitable for heart transplantation, this still leaves a large number of potential recipients.

The main constraints on the development of cardiac transplantation on a large scale are limited funds and limitation of the supply of suitable donor organs. During the first year of our programme the lack of donor hearts proved nearly insurmountable, but there has been a gratifying change in public attitude during the last six months, and heart donation now usually results from a specific request from the relatives that this be considered. Estimates of the cost of heart transplantation suggest that the cost of the first transplant year, including the costs of assessing recipients not necessarily transplanted, is about four times the cost of a major routine open heart operation. These costs, however, would be much reduced if an effective non-toxic immunosuppressive agent were developed, enabling a shorter stay in hospital and fewer postoperative investigations.

In the meantime, however, it would seem reasonable to continue with a cautious and careful evaluation of the potential benefits from heart transplantation. This demands strong teamwork and a high degree of commitment and expertise from

ADDENDUM.—Since submission of this paper there have been two more deaths. A 52-year-old man died suddenly from a dysrhythmia four months after operation and a 16-year-old boy died in hospital two months after transplantation. He developed fits and unconsciousness one week after operation and eventually died from pulmonary infection.

all the related specialties such as immunology, bacteriology, radiology, pathology, and cardiac anaesthesia, in association with skilled medical and nursing care.

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Attenuation of hypotensive effect of propranolol and thiazide diuretics by indomethacin

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Summary and conclusions

The effects of 100 mg indomethacin daily for three weeks on blood pressure and urinary excretion of prostaglandin $F_{2\alpha}$ were studied in a double-blind, placebo-controlled comparison of two groups of patients with essential hypertension, eight receiving propranolol and seven thiazide diuretics. Compared with placebo, adding indomethacin to the patients' established antihypertensive treatment increased blood pressure by 14/5 mm Hg supine and 16/9 mm Hg erect in the patients receiving propranolol, and by 13/9 mm Hg supine and 16/9 mm Hg erect in the patients receiving thiazide diuretics (all $p \leq 0.05$). The excretion of the major urinary metabolite of prostaglandin $F_{2\alpha}$ was reduced by 67% in the propranolol-treated patients and by 57% in those receiving a thiazide diuretic. Body weight increased by 0·8 kg (propranolol) and 1·1 kg (thiazide diuretic) when indomethacin was given, but there were no significant changes in creatinine clearance, urinary sodium excretion, or packed cell volume in either treatment group.

These results suggest that products formed by the arachidonic acid cyclo-oxygenase contribute to the regulation of blood pressure during treatment with both propranolol and thiazide diuretics. Inhibition of the cyclo-oxygenase with indomethacin partially antagonises the hypotensive effect of these drugs.

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Introduction

Beta-receptor-blocking drugs lower systemic blood pressure, but the mechanism is not established. Negative cardiac chronotropic[1] and inotropic[2] effects, anti-renin effects,[3] and central nervous system effects[4] may all contribute to their hypotensive action in man. Initially, systemic vascular resistance is raised after beta-receptor blockade.[5] During chronic beta-receptor blockade, however, systemic vascular resistance often falls towards pre-treatment values, despite the persistently reduced cardiac output.[6 7] Whether this is due to a change in the sensitivity of the baroreflex arc,[8] down-regulation of adrenergic receptors,[9] reduced concentrations of angiotensin II, or some other mechanism is uncertain. Durão *et al*[10] proposed that chronic beta-receptor blockade may stimulate formation of vasodilator prostaglandins, since indomethacin, a potent inhibitor of prostaglandin synthesis,[11 12] can attenuate the hypotensive effect of chronic propranolol treatment in man.[10] We therefore undertook a study to examine the specificity of this effect. In two groups of patients with essential hypertension, one receiving propranolol, the other a thiazide diuretic, we compared the effects of adding 100 mg indomethacin daily or placebo over three weeks in a randomised, cross-over study. A major urinary metabolite of prostaglandin $F_{2\alpha}$, prostaglandin $F_{2\alpha}M$, was measured as an index of the inhibition of total prostaglandin synthesis.

Patients and methods

We selected for the study 15 patients with mild essential hypertension. Supine blood pressure was controlled at 150/95 mm Hg or below with single-drug treatment. Eight patients (five men, three women) were being treated with 60-320 (mean 168) mg propranolol daily and seven (five men, two women) with a diuretic (five were receiving 5-10 mg bendrofluazide and two one to two tablets of Moduretic (amiloride 5 mg and hydrochlorothiazide 50 mg per tablet) daily). The propranolol-treated group were aged 50 ± 4 years and the diuretic-treated group 57 ± 3 years. The patients were otherwise healthy and, in particular, free from dyspeptic symptoms. Blood urea