PAPERS AND ORIGINALS

Long-term survival after orthotopic and heterotopic cardiac transplantation

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Summary and conclusions

Five long-term survivors of heart transplantation were reinvestigated. Two patients had undergone orthotopic heart transplantation over 11 and 9 years earlier and constitute two of the world's longest-surviving patients after this procedure. Three patients had undergone heterotopic heart transplantation (one left heart bypass alone and two biventricular bypass) four to six years earlier. Four of the five patients had had only one or no documented acute rejection episodes. Three had been given blood transfusions. None had had particularly good tissue matching in relation to the donor on HLA typing. All five patients were leading full and active lives. At review two patients had significant coronary artery disease, one severe, presumably due to chronic immune-complex deposition.

Heart transplantation remains a major undertaking, but it can offer the patient many years of good-quality life.

Introduction

From 1967 to 1973, 11 patients underwent orthotopic heart transplantation (10 men, 1 woman; age range 36 to 63 years, average 49 years) at Groote Schuur Hospital.[1] Four patients survived more than one year, and two patients remain alive 11 and 9 years after operation.

In the five and a half years from November 1974 to May 1980, 30 patients (27 men, 3 women; age range 14 to 52 years, average 37 years) underwent heterotopic heart transplantation.[2] One patient underwent a second transplant 18 months after his initial operation. Fifteen (50%) were still alive six months to almost five and a half years after transplantation. One-year survival was 64%; three out of six patients have survived more than four years.

The two patients with orthotopic grafts represent two of the world's longest survivors after this operation. The longest survivor of heterotopic heart transplantation, now in his sixth year, was one of only two patients who underwent left heart bypass alone.[3] In this operation the anastomoses performed were donor-to-recipient left atria and aortae; donor heart coronary sinus return was channelled back to the recipient's circulation by anastomosing the donor pulmonary artery to the recipient right atrium. In the two other patients with heterotopic grafts who have survived more than four years both right and left ventricles were supported by the donor heart.[3] The donor heart was connected in parallel to the recipient heart by anastomoses between the two left atria, superior vena cavae, aortae, and pulmonary arteries (using a conduit of either donor aorta or Dacron); this has been the operation of choice in subsequent patients.

All five of these patients were recently admitted for investigation. All patients underwent routine right and left heart catheterisation via the transfemoral route in the supine position under light sedation. The zero reference was taken at the mid-thoracic level. Left ventricular ejection fractions were calculated from left ventricular cine-angiograms in the right oblique projection and in the posteroanterior projection for the donor hearts of cases 4 and 5. Selective coronary arteriography (Judkins) and donor right or left ventricular endomyocardial biopsy were performed in all cases.

Case 1

The longest surviving patient was a coloured woman with a long history of rheumatic heart disease, two previous mitral valvotomies, and subsequent mitral valve replacement. In April 1969, at the age of 37, she underwent orthotopic heart transplantation after being admitted in refractory cardiac failure with a normally functioning prosthesis. Her postoperative recovery was complicated by pneumonia, hepatitis, leg myopathy, and aural and visual hallucinations. She has taken azathioprine and prednisolone for immunosuppression.

She suffered several early acute rejection episodes but has since

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enjoyed a full, active life. Major late complications have included avascular necrosis of the right humeral head and both tibiae, presumably caused by steroid therapy, though it has not seriously limited her movement. She also required truncal vagotomy and pyloroplasty for acute perforation of a duodenal ulcer in 1978. Urinary tract infections, aseptic dysuria, and backache from osteoporosis have troubled her occasionally, and she has needed skin grafting for leg ulceration more than once. She also developed a cataract, mild glaucoma, and underwent cholecystectomy for gall stones in 1979.

At review she appeared thin with no obvious Cushingoid features and was in sinus rhythm with a blood pressure of 100/70 mm Hg. The venous pressure was raised 4 cm; the tip of the liver was palpable. The pulmonary second sound was palpable but there was no right ventricular lift. A soft apical fourth heart sound could be heard and the pulmonary second sound was prominent. In the second left interspace a short mid-systolic murmur was audible.

Electrocardiographic and radiographic features and the results of cardiac catheterisation are shown in the table. Histological examination of a right ventricular endomyocardial biopsy specimen showed minimal fibrosis with normal blood vessels and no other significant abnormality. Scored on the basis of the scoring system of Rose and Uys[4] acute rejection activity was assessed as 0.

Her drug treatment included daily azathioprine 150 mg, methylprednisolone 10 mg, digoxin 0·25 mg, frusemide 60 mg, potassium and calcium supplements, and cimetidine.

Case 2

This Caucasian man underwent orthotopic heart transplantation for ischaemic heart disease in May 1971 at the age of 45 years. During induction of anaesthesia for transplantation he suffered repeated ventricular fibrillation; the operation itself was uneventful. He suffered no postoperative complications and has had no documented rejection episodes. Azathioprine and prednisolone have been continued since operation.

He returned to full-time employment within three months of his operation and has led a normal life. Backache in 1973 was related to compression of the 4th to 9th thoracic vertebrae due to osteoporosis. He had no other late complications. He has been mildly hypertensive for some years and took methyldopa; recently he developed intermittent claudication in both calves.

At review he was overweight, not obviously Cushingoid, and had no evidence of cardiac failure. His blood pressure was 140/90 mm Hg. Heart sounds were soft and there were no murmurs or added sounds. There were no palpable pulses below the femoral arteries in either leg, but there was no overt evidence of leg ischaemia.

Electrocardiographic and radiographic features and the results of cardiac catheterisation are shown in the table. Endomyocardial biopsy showed some hyaline thickening of the small vessel walls, but no other evidence of rejection (score 1·5).

His drugs were azathioprine 200 mg daily, prednisolone 5 mg twice a day, sulphinpyrazone 200 mg three times a day, methyldopa 250 mg four times a day, and standard doses of clofibrate, Moduretic, and antacids.

Case 3

This 47-year-old Caucasian man had had a long history of rheumatic heart disease[3] and despite two aortic valve replacements developed intractable left ventricular failure. In December 1974 a left ventricular bypass[3] was performed using a cardiac allograft. A small aortic paraprosthetic leak was also repaired and the poppet of the University of Cape Town prosthesis replaced. His early recovery was uneventful. Only one significant acute rejection episode was documented at six months. He remained well for four months, when he experienced the first of several attacks of paroxysmal ventricular tachycardia of his own heart, requiring electrical defibrillation and drug treatment.[5]

In May 1976 he was admitted with bacterial endocarditis due to *Staphylococcus aureus*. He then suffered an acute myocardial infarction in his own heart. Cardiac catheterisation showed that the prosthesis was not opening, probably because of a thrombus. The patient's own left ventricle was not working. The prosthesis was excised, the aortic root closed with the anterior leaflet of the mitral valve, the mitral valve orifice closed, and left ventriculectomy performed in June 1976 in an effort to remove the source of the *Staphylococcus aureus*, excise the focus of the recurrent episodes of ventricular tachycardia, and remove a potential source of systemic emboli. One month later a bleeding peptic ulcer was successfully treated medically.

Since then he has remained well and active. At review he had no exercise limitation or other symptom but was overweight with minimal Cushingoid features. His pulse was regular at 90/min at rest, venous pressure raised 3 cm, blood pressure 120/80 mm Hg. He had some

Investigations in two patients with orthotopic and three patients with heterotopic cardiac transplants

	Case 1	Case 2	Case 3	Case 4	Case 5
Electrocardiogram	SR, rate 98/min, axis +120°, incomplete RBBB	SR, rate 78/min, axis −20°, incomplete RBBB, minor ST and T-wave changes	*Recipient* SR, rate 67/min, axis indeterminate, no precordial R-wave progression *Donor* SR, rate 94/min, axis +70°, normal	*Recipient* SR, rate 68/min, axis +15°, old anterior and inferior infarcts *Donor* SR, rate 100/min, axis indeterminate, complete RBBB	*Recipient* SR, rate 114/min, left axis deviation −55°, incomplete LBBB *Donor* SR, rate 90/min, axis +30°, normal
Chest radiograph	Slight pulmonary congestion	Unremarkable	Cardiac shadow showing donor heart and absence of recipient left ventricle	Recipient and donor heart shadow, otherwise normal	Recipient and donor heart shadow, otherwise normal
Cardiac catheter pressures (mm Hg):					
	Phasic *Mean*	*Phasic* *Mean*	*Phasic* *Mean*	*Phasic* *Mean*	*Phasic* *Mean*
Right atrial pressure	a15 v14 13	a6 v8 7	(*R*) 6	(*R*) 8 (*D*) 8	(*R*) 8 (*D*) 8
Right ventricular pressure	41/4–13	33/4–8	44/2–8 (*R*)	32/8–12 (*R*) 32/8–12 (*D*)	34/2–8 (*R*) 34/2–8 (*D*)
Pulmonary artery pressure	41/25 29	33/18 23	44/22 (*R*) 24	32/17 22	34/22 30
Pulmonary artery wedge pressure	a20 v38 29	a15 v14 12	a16 v14 (*R*) 15		10
Left ventricular pressure	112/11–23	145/5–11	128/11–16 (*D*)	128/16 (*R*) 132/16 (*D*)	73/12 (*R*) 95/10 (*D*)
Aortic pressure	112/75 93	145/90 112	128/88 (*C*) 110	132/98 (*C*) 112	95/65 (*C*) 73
Cardiac output (l/min)	5·3	5·3	5·7	8·1	4·4
Cardiac index (l/min/m²)	3·6	2·7	2·6	4·2	2·3
Pulmonary vascular resistance (units)	1·0	2·0	1·6	1·2	1·1
Systemic vascular resistance (units)	16·0	21·0	19·4	13·0	15·0
Ejection fraction (%)	45	73	72	39 (*R*) 50 (*D*)	10 (*R*) 56 (*D*)
Left ventricular angiogram	Normal volume, inferoapical dyskinesia	Normal volume, good contractility	Normal volume and contractility	Recipient: grossly dilated, global dyskinesia; donor: normal volume and contractility	Recipient: grossly dilated, akinetic; donor: normal volume and contractility
Coronary angiogram	RCA occluded, LAD 60% proximal stenosis, LCCA diffuse non-critical disease	Normal	PDA 60% stenosis, LAD and LCCA severe diffuse disease	Recipient: not done, donor: normal	Recipient: not done, donor: normal

SR = Sinus rhythm. RBBB = Right bundle-branch block. LBBB = Left bundle-branch block. RCA = Right coronary artery. LAD = Left anterior descending coronary artery. LCCA = Left circumflex coronary artery. PDA = Posterior descending branch of right coronary artery.
(*R*) = Recipient. (*D*) = Donor. (*C*) = Common.

periorbital oedema and minimal ankle oedema. His apex beat was to the right of the sternum. Donor first and second heart sounds appeared normal; occasional added sounds from the recipient right heart were audible. Electrocardiographic features and findings on cardiac catheterisation are listed in the table. We could not perform full right and left heart catheterisation of the donor heart because there were no right-sided anastomoses between donor and recipient organs. Donor left ventricular endomyocardial biopsy showed minimal to mild acute rejection (score 2). The myofibres were basically well preserved, though some appeared vacuolated. There were occasional interstitial aggregates of mononuclear cells and some fibrosis.

His daily drug therapy consisted of azathioprine 250 mg, methylprednisolone 16 mg, sulphinpyrazone 600 mg, digoxin 0·25 mg, frusemide 80 mg, potassium supplements, cimetidine, and antidepressants.

Case 4

This Caucasian man with intractable failure from ischaemic heart disease underwent heterotopic heart transplantation with biventricular bypass at the age of 32 years in December 1975. Immunosuppression has been with azathioprine, methylprednisolone, and initially antilymphocyte globulin. On the eighth day after operation cardiac catheterisation showed severe failure of both donor and recipient right and left ventricles with right ventricular end-diastolic pressures of 32 mm Hg and a mean capillary wedge pressure also of 32 mm Hg. Donor right ventricular endomyocardial biopsy showed only mild oedema. Clinically he steadily improved, and this episode was never fully explained. He suffered no definite episodes of acute rejection.

His postoperative progress was complicated by a purulent, retrosternal wound infection which twice required exploration and drainage and prolonged antibiotic treatment. Late complications included sternal osteochondritis and dizzy spells and brief loss of consciousness of indeterminate cause in 1977, since when he has been taking both anticoagulants and phenobarbitone.

At review he was fit and extremely active, working as a fisherman, pulling in catches of up to 82 kg. Examination showed a normal appearance, an irregular pulse due to the two beating hearts, a blood pressure of 120/85 mm Hg, impalpable apex beats, and no signs of failure. Normal donor heart sounds could be heard with no murmurs; there was a recipient heart fourth sound with no murmurs.

Electrocardiographic, radiographic, and cardiac catheterisation findings are shown in the table. Biopsy sections of right ventricular myocardium showed evidence of minimal rejection, with occasional myofibre degeneration and mononuclear cells (score 2).

His drug treatment consisted of daily azathioprine 250 mg, methylprednisolone 14 mg, dipyridamole 400 mg, warfarin, phenobarbitone, and antacids.

Case 5

This Caucasian man developed a cardiomyopathy and underwent biventricular bypass with a heterotopic transplant in January 1976 when he was 25 years old. His early postoperative recovery was uneventful. Immunosuppression consisted of azathioprine, prednisolone, and antilymphocyte globulin. In October 1976 he discontinued his medication and underwent severe acute rejection; the donor heart deteriorated to the point of ventricular fibrillation, requiring electrical defibrillation and considerable antirejection treatment. He recovered completely.[6]

Since then he has remained well and active. At review he looked normal and had a blood pressure of 120/80 mm Hg and no signs of failure. Normal donor heart sounds could be heard with no murmurs.

The electrocardiographic (fig 1) and radiographic (fig 2) features are detailed in the table, together with the results of cardiac catheterisation. Right ventricular endomyocardial biopsy showed no significant rejection changes. The myofibres were well preserved with only an occasional mononuclear cell in the interstitium. The smaller coronary vessels had prominent media and there was some intimal thickening from cell proliferation (score 0·5).

His drug treatment consisted of daily azathioprine 200 mg, prednisolone 10 mg, dipyridamole 400 mg, digoxin 0·25 mg, warfarin, and antacids.

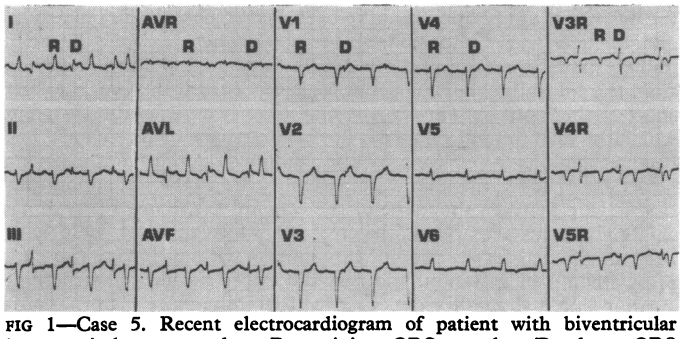

FIG 1—Case 5. Recent electrocardiogram of patient with biventricular heterotopic heart transplant. R=recipient QRS complex; D=donor QRS complex.

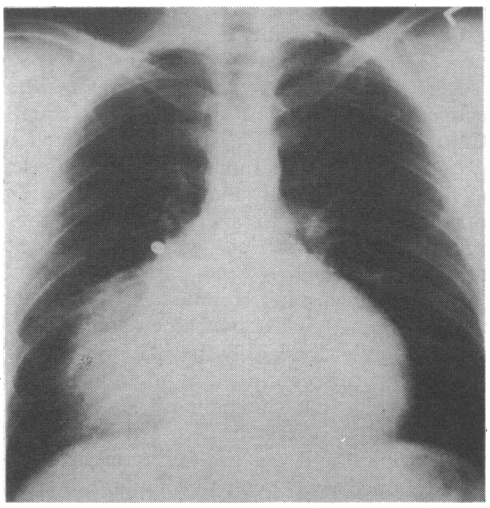

FIG 2—Case 5. Recent posteroanterior chest radiograph of patient with biventricular heterotopic heart transplant. The "button" is an atrial pacing electrode used in early postoperative period.

Discussion

All five patients have undoubtedly had their lives prolonged and have experienced a good quality of life since operation. The long survival of these patients may be related to several factors. The relative absence of acute rejection episodes in four cases is obviously important, although such episodes, particularly in the case of orthotopic grafts, were less well recognised at the time of the operations than they would be today. Of the two patients with orthotopic transplants, one (case 1), who had multiple acute rejection episodes, has advanced diffuse coronary artery disease, whereas the other, who had no rejection episodes, has minimal changes. If her heart were not denervated the first patient would probably now be troubled by angina. The risk of sudden cardiac arrest must be high, and we are therefore considering whether to advise her to undergo retransplantation, possibly with a heterotopic heart.

The first of the three patients undergoing heterotopic heart transplantation has fairly advanced coronary artery disease, but left ventricular function is well preserved. Tissue typing was relatively primitive at the time of the two orthotopic heart transplants, but none of the five patients had a particularly well-matched heart on HLA typing. One major series of orthotopic heart transplantation has found no correlation between tissue typing and survival.[7] Before their transplantation two patients (cases 1 and 3) had undergone previous open heart surgery and one (case 4) had received a blood transfusion, and the Stanford group have reported improved survival in patients who have received previous blood transfusions.[7]

Three patients (cases 2, 3, and 5) showed no significant change in electrocardiographic voltage after the early postoperative

period. In case 1 the electrocardiogram was stable and normal until the seventh year, when the patient developed right axis deviation and incomplete right bundle-branch block unrelated to any detectable clinical event; there has been no further change. Case 4 has shown a right bundle-branch block pattern in the donor heart since the episode of biventricular failure at the end of the first week after operation.

Haemodynamic function in these patients may be affected by the high steroid dose used for immunosuppression, the presence of donor heart denervation, and pre-existing pulmonary vascular changes.[8] The mild increase in right heart pressures in two of our patients (cases 1 and 5) could have been related to pulmonary vascular changes, steroid-induced hypervolaemia, or chronic rejection, the functional effects of which may be predominantly right-sided.[9 10] Left ventricular end-diastolic pressure (LVEDP) was moderately raised in case 1 because of the left ventricular dysfunction and extensive coronary artery disease, but it was normal or only marginally raised in the others. Preoperative LVEDP at rest in case 4 was grossly raised at 38 mm Hg, reflecting severe left ventricular disease. At review the LVEDP in both recipient and donor left ventricles was equal and only slightly raised at 16 mm Hg. This is to be expected since both left ventricles are filled from a functionally common left atrium. Preferential filling of the healthy and presumably more compliant donor ventricle will occur, thus decompressing the diseased, non-compliant recipient ventricle and equilibrating the end-diastolic pressures.

In all three patients with heterotopic heart transplantation the recipient heart continued to function, albeit poorly. In the patient with a left heart bypass alone, only the right ventricle of his own heart remained, but this continued to maintain his pulmonary circulation. The help that the patient's own heart can give, particularly during episodes of acute rejection, has been emphasised elsewhere[2] and was life-saving in case 5, where the donor heart developed ventricular fibrillation during a rejection episode.[6]

We believe that anticoagulation with warfarin is essential in patients with heterotopic grafts to diminish the risk of pulmonary or systemic emboli from thrombus which may form in the poorly contracting ventricles of the recipient heart. We also think that the presence of a prosthetic valve in the recipient heart is a contraindication to heterotopic heart transplantation as it may provide a focus for thrombus formation or infection, as in case 3. An orthotopic heart transplant should be carried out in such cases or the prosthetic material should be removed, though this will inevitably mean that a procedure such as left ventriculectomy is also needed.

The other late complications met in this small group were those associated with long-term steroid therapy. Nevertheless, although heart transplantation remains a major undertaking for both patient and surgical team, it can offer the patient many years of good quality life.

We thank the many members of the medical, nursing, and laboratory staff of Groote Schuur Hospital and the University of Cape Town Medical School who have contributed to the care of these patients.

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ONE HUNDRED YEARS AGO A seaman, aged 28, came to me a few days ago with the following history. Three weeks since, when with his ship off Greenock, he went ashore, being somewhat the worse for drink at the time, to look for a shipmate. As he was gazing into the window of a factory, a workman thrust something into his eye. At first, he thought it had been merely his finger. Feeling pain in the eye, he applied to a medical man, who ordered him poultices and a wash of nitrate of silver. At times he felt a dull aching, which gradually became worse. A week later, on looking in the glass, he could see something in the eye, and pulled out a piece of pipe-stem broken in halves down the centre, which, from his description, would appear to be rather over one-third of an inch in length. He could see with the eye; but, still feeling pain, he was anxious to have something further done, and applied for advice at a hospital, but was told there was nothing the matter with the eye.

On examination, there was seen to be much chemosis, the conjunctiva—chiefly over the lower part of the globe—being swollen into thick projecting folds; and, on depressing the lower lid, a prominence of the membrane was observed, situated near the inner canthus, but covered by the lid when *in situ*. A hard body could be felt under this conjunctival swelling. The eye itself was forced somewhat backwards and upwards, but, as far as could be seen, was itself uninjured. A speculum was introduced to keep the lids well apart; and, on snipping through the mucous membrane with a pair of scissors, I was able to see occasionally a white object, which constantly vanished and reappeared with the movements of the eyeball. After several trials, I succeeded, with a fine sinus-forceps, in getting a good hold of it, and withdrew a piece of clay pipe-stem over three-quarters of an inch in length. One end was rounded, the other was broken sharp and somewhat jagged. A graduated wet compress was applied over the eye, and the man was ordered to return next day. The subsequent progress of the case was satisfactory. Two minute particles of the pipe were removed a few days later from the mouth of the wound, which shortly afterwards closed, leaving the eye entirely uninjured. The exact dimensions of the piece of pipe-stem were as follow: greatest length, seven-eighths of an inch; diameter at broad extremity, a quarter of an inch; at narrow end, three-sixteenths of an inch.

The eye in this case had undoubtedly a narrow escape from complete destruction. From the way in which the injury occurred, the globe of the eye must, in my opinion, have been first struck by the pipe-stem, and, by its elasticity, slipt aside and escaped puncture, while the stem, gliding past it, perforated the conjunctiva near its point of reflexion from the lid to the globe, and buried itself beneath the eye, breaking short at the moment. However it may have been with the fragment which the man himself removed, the larger piece which remained had become completely covered by the conjunctiva, the wound having healed, and the fragment being fairly embedded in the soft submucous tissue lying between the globe of the eye and the floor of the orbital cavity. It seems remarkable that this large foreign body could have been so situated for a period of three weeks without having caused a great amount of irritation, and that the eye itself and the structures surrounding it should have escaped with nothing more than the comparatively slight inconvenience which the patient seems to have experienced. (*British Medical Journal*, 1880.)