

## Original Article

# Early and late outcomes after heart transplantation in a low-volume transplant centre

Alexander Manché

## Abstract

Early (one year) and late (15 year) outcomes after heart transplantation in Malta were evaluated by means of a retrospective analysis of mortality and morbidity, derived from the transplant database. Fifteen transplants were performed with an 87% operative and one-year survival and an 80% 15-year survival. Four patients experienced complications necessitating major surgical interventions and 5 further patients required hospital admission for other complications. Four patients never required hospital admission after their transplant. Twelve long-term survivors enjoy an unrestricted life, whereas one patient is troubled with recurrent gout. Results of heart transplantation can be gratifying, even when performed in a low-volume centre.

## Introduction

Cardiac transplantation may become the treatment of choice for selected patients suffering from severe, end-stage heart failure, unresponsive to maximal medical therapy. In recent years worldwide transplantation rates have reached a plateau, with potential recipients outstripping available donors by a factor of ten.<sup>1</sup> Some countries, such as the UK, have experienced a decline of 50% over the last ten years, triggering a review of the number of transplant centres.<sup>2</sup> Recent evidence has linked early survival to transplant centre volume, citing a higher risk of early mortality in lower-volume centres.<sup>3</sup>

This study sets out to demonstrate that short- and long-term survival can be achieved in a low-volume transplant centre.

## Keywords

Heart transplant, outcome, transplant centre

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The population of Malta is close to 400,000 and cardiac transplants are performed at a rate of approximately one per year. The Maltese cardiac transplant program qualifies as a very low-volume centre and figures are not likely to increase due to global as well as local factors. Six adult transplant centres support a country like the UK, with a population of 60 million, with specialist skills and resources spread across the country. One hundred and twenty transplants were performed in 2009-2010, a rate of 2 per million population (range 4-23 transplants per unit).<sup>4</sup> Italy and Germany both support 8 heart transplant units with similar transplant rates. Our local rate of transplantation is not significantly different.

## Methods

### Preparation

The local transplant program began in 1995 soon after the establishment of our general cardiothoracic program. Protocols were drawn up and a pathologist was trained overseas in the interpretation myocardial biopsies. The laboratory made plans for the provision of an emergency service for cyclosporine level estimation. Special arrangements were made for a single intensive care room with reverse barrier nursing facilities. Close collaboration with cardiology was established for the serial measurements of pulmonary vascular resistance and post-operative myocardial biopsies. A suitable recipient was identified and a donor became available on the 25th September 1996, when the first successful orthotopic transplant was performed.

### Recipients

All potential recipients were referred to the program either via the cardiology department or were identified by us as transplant candidates after they had been referred for a diverse surgical procedure. These latter patients were then referred to cardiology for further evaluation before being considered potentially suitable candidates. In the late 1990's patients were referred after failure of standard medical treatment for heart failure, be it secondary to ischaemic heart disease or cardiomyopathy. In recent years more patients have enjoyed the benefits of improved medical treatment with ACE inhibitors, spironolactone, beta-blockers and ivabradine, as well as re-synchronisation therapy, sometimes combined with an implantable defibrillator. An improvement in their heart failure class has often translated into a delay in placing on, or a withdrawal of these patients from our active list.

## Donors

All potential donors were referred to us from the general intensive care unit after they had been declared brain dead and consent for organ donation had been obtained. Qualified specialists performed the brain death tests on two separate occasions, after all biochemical and other relevant abnormalities had been corrected. Once a donor's organs were deemed acceptable for transplantation, a suitable recipient was alerted and admitted to hospital when a further right heart study was performed where indicated. Coordination with other retrieval teams, often from abroad, was effected via the transplant coordinator and all interested parties then worked towards a common goal and a set program. In Malta we practice an opt-in system of donation.<sup>5</sup>

## Method of transplantation and aftercare

All patients received an orthotopic transplant and all donor hearts were retrieval locally, obviating the need for distant procurement. Surgery was performed at normothermia and according to the methods described by Brock and Shumway.<sup>6</sup> Temporary dual chamber pacing leads were routinely implanted and the patient was nursed post-operatively in a single cubicle with reverse barrier precautions. Triple therapy immunosuppression was administered and prolonged inotropic and chronotropic support was usually necessary. Patients were discharged from hospital when they were mobile and after two satisfactory biopsy results. Aftercare was comprehensive, with open channels for patient communication, regular follow-up, and programmed biopsies. Our department worked closely with the departments of cardiology, infectious diseases and renal medicine.

## Haemodynamic measurements

Pulmonary vascular resistance (PVR) was calculated by measuring the trans-pulmonary gradient (mean pulmonary artery pressure minus pulmonary capillary wedge pressure) in mmHg, and dividing this by the cardiac output (measured by the thermodilution method) in l/min. PVR is given in mmHg.min/l, also known as Wood units.

## Statistics

Continuous variables were expressed as mean±standard deviation (SD) and the Student's t-test was used to compare means. SPSS 13.0 (Chicago, IL) was used for computation. Statistical significance was accepted at a level of  $p < 0.05$ .

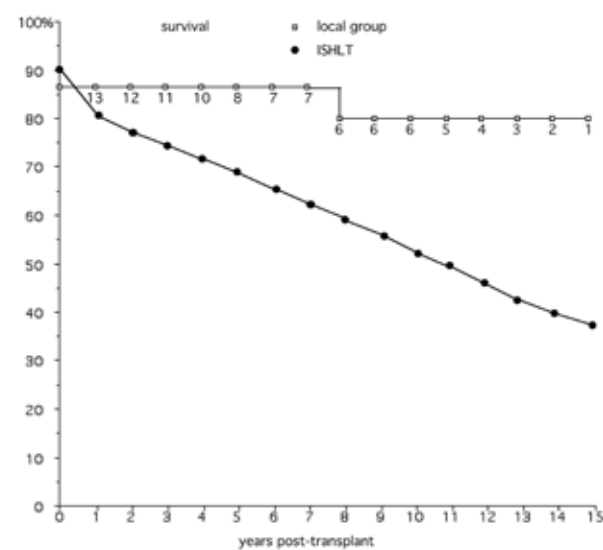
## Results

Fourteen transplants were performed in Malta, and a further transplant performed jointly at Great Ormond Street Hospital, London, on a Maltese adolescent with congenital heart disease, who receives his medical follow-up locally.

## Mortality

The survival curve is shown in Figure 1. Early survival was 87% and late survival, at fifteen years 80%.

Figure 1: Actuarial survival



Legend: Figures below graph for local group show numbers of patients at risk. ISHLT: International Society for Heart and Lung Transplantation Registry

There were two operative deaths, both due to pulmonary hypertension and acute right ventricular failure.<sup>7</sup> One patient was a 23-year-old man of South American origin who had dilated cardiomyopathy and a pulmonary vascular resistance of 3.6 Wood units. He was in cardiogenic shock on an intra-aortic balloon pump at the time of transplantation. The other patient was a 62-year-old man who had undergone a coronary bypass operation four years previously and presented with heart failure. His pulmonary vascular resistance was 3.0 Wood units.

One late death occurred in a 56-year-old man (patient 6, Table 1), eight years after transplantation, due to graft vasculopathy<sup>8</sup> and heart failure. This patient required several admissions for treatment of heart failure during his last year of life and underwent coronary angioplasty with stenting.

## Major morbidity

Patient clinical summaries are presented in Table 1. Nine patients were readmitted at some time in their post-operative course.

Seven patients required further surgery, four after major complications, as follows:

- Patient 4 developed post-operative suppurative mediastinitis and underwent re-sternotomy, debridement and irrigation, with good result.
- Three patients required major abdominal surgery:
  - Patient 10 underwent appendectomy for acute appendicitis one year after transplantation. He presented with a purulent discharge from the biopsy entry-point in his groin.
  - Patient 11 underwent salpingo-oophorectomy for a pelvic abscess two years after transplantation. She presented with pyrexia of unknown origin and ultrasound revealed Fallopian tube pathology.

**Table 1: Clinical summary**

Patient	Age	Transplant year	Rejection	Creatinine	Admission	Complications
1	52	1996	nil	-	+	skin carcinoma*, gout
2	54	1997	1	+	+	depression, gout, prostatitis, mild CAD
3	52	1998	nil	+	+	CAPD*, BCC*
4	62	1999	nil	-	-	mediastinitis**, gout, orchitis
5	15	2000	nil	-	-	nil
6	48	2000	2	-	+	graft vasculopathy, CMV, died at 8 years
7	48	2001	nil	-	-	nil
8	57	2005	1	-	+	pneumocystitis jiroveci, TURP*
9	60	2006	1	-	-	herpes zoster
10	63	2007	1	-	+	appendicitis**, severe gout
11	34	2009	1	-	+	pelvic abscess**, CMV
12	57	2010	nil	-	+	CMV
13	62	2011	nil	-	+	diverticulitis**, CMV

\* requiring surgery \*\* requiring major surgery

- Patient 13 underwent emergency left hemicolectomy for diverticulitis complicated by massive intestinal bleeding, six months after transplant. His colostomy was reversed successfully 6 months later.
- Three further patients required surgery:
  - Patient 1 required several excisions of cutaneous basal cell and squamous cell carcinomas, as well as cervical lymph node biopsy and radiotherapy, fourteen years after transplant. His condition is now under control.
  - Patient 3 required excision of a basal cell carcinoma, as well as insertion of a catheter for peritoneal dialysis twelve years after transplant. He is awaiting kidney transplantation.
  - Patient 8 required trans-urethral resection of the prostate for benign disease, three years after transplant.
- Other hospital admissions were due to the following:
  - Patient 2 required admission for acute renal failure as well as non-compliance with medication, secondary to depression, ten years after transplant. This was successfully resolved and he remains well.
  - Patient 8 required admission for treatment of Pneumocystis jiroveci pneumonia, while patients 11, 12 and 13 required readmission for treatment of cytomegalovirus infection/reactivation, all within six months after transplant.

#### Post-operative course

No formal quality of life assessment was undertaken.<sup>9</sup> Twelve patients enjoy an unrestricted life. Patient 10 suffers from recurrent episodes of gout, curtailing quality of life and requiring medication for symptom relief.

Four males are gainfully employed and one female leads a busy life as a housewife. Eight patients have traveled abroad since their transplant, five of these on multiple occasions. Four patients suffered no major late complications and have never been readmitted to hospital since their transplant, except as a day case for myocardial biopsy and coronary angiography as indicated. Although four patients suffered complications requiring major surgery, three of them experienced short-lived morbidity and their post-operative recovery was swift. Patient 13 was subjected to a colostomy for 6 months before this was successfully reversed.

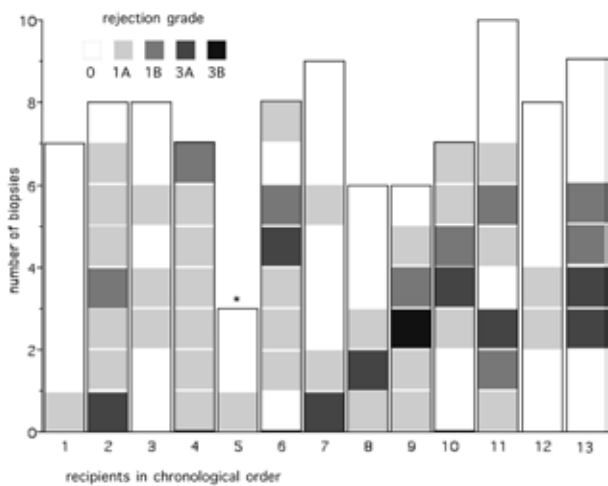
#### Myocardial biopsies

The number of biopsies performed during the first year averaged 8 (Figure 2). Patients generally underwent one biopsy per annum in subsequent years. Patients who developed serious rejection of grade 3A and above had significantly higher white cell counts as a group ( $6.71 \pm 2.19 \times 10^9/l$ ), than those that did not develop serious rejection ( $4.96 \pm 1.62 \times 10^9/l$ ,  $p < 0.0001$ ).

#### Coronary angiography

All patients underwent coronary angiography on one or more occasions once three years had elapsed from their transplant. Of the ten patients who underwent angiography, patient 6 had severe diffuse coronary artery disease consistent with graft vasculopathy. He had suffered two episodes of severe rejection after poor compliance with his immunosuppressant medications. He underwent angioplasty and stenting but his disease progressed and he died 8 years after his transplant. Patient 2 was found to have moderate disease in two obtuse marginal arteries and remains under review. The eight other coronary angiograms were either normal or showed mild, non-significant disease.

**Figure 2: Biopsies performed during the first year**



\* four further biopsies performed at GOS Hospital, London

### Renal function

There was a gradual rise in creatinine levels with passing years (Figure 3). Two patients developed a creatinine level over 300µmol/L and one is on chronic ambulatory peritoneal dialysis awaiting renal transplantation. Cyclosporine toxicity did not play a role as levels were lower in these two patients (104±44 ng/ml versus 118±35 ng/ml in the rest).

### Immunosuppression

All patients were started on triple immunosuppression therapy with intravenous methylprednisolone, and oral azathioprine and cyclosporine. Within a few days the steroids were changed to oral prednisolone, which was tailed off gradually over a mean of 4 years (range 2-7 years), depending on biopsy results and clinical course. Azathioprine was changed to mycophenolate sodium in one patient because of hepatotoxicity. In another patient with gout, azathioprine was also temporarily changed to mycophenolate when allopurinol was introduced but renal function deteriorated and medication was reverted with improvement. A third patient also discontinued azathioprine because of pancytopenia and subsequently had his cyclosporine changed to sirolimus after he developed squamous cell carcinoma of the skin. All other patients were managed on long-term azathioprine and cyclosporine.

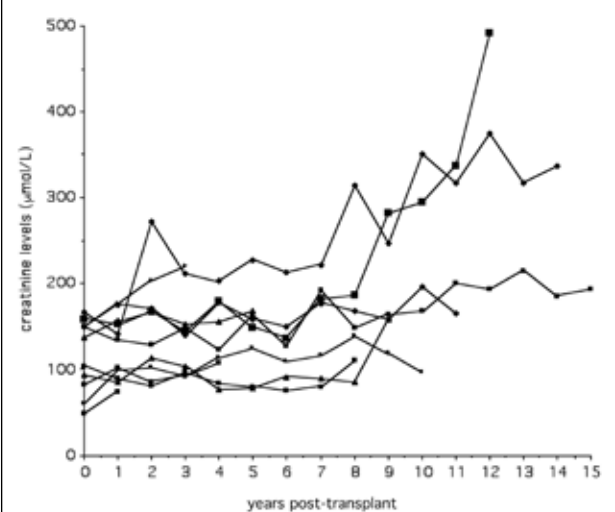
### Other medications

Standard medications included aspirin, nystatin syrup, co-trimoxazole, perindopril, and statins. Fluvastatin was the preferred statin in view of possible interactions of other statins with cyclosporine.<sup>10</sup> Angiotensin receptor blockers have recently been withheld because of reports of a possible increased incidence of thoracic tumours in smoking transplantees.<sup>11</sup>

### Discussion

Declining transplant numbers in the UK, blamed on a scarcity of intensive care beds, have triggered a downward

**Figure 3: Creatinine levels**



review of the number of transplant centres. The UK Health Department stated that surgeons might experience difficulties in maintaining competence in a contracting practice.<sup>12</sup> A study by Shuhaiber et al<sup>3</sup> concluded that early mortality was higher in very low-volume transplant centres when compared with higher volume centres. A similar study by Hosenpud et al<sup>13</sup> showed a significantly higher early and one-year mortality in centres performing fewer than nine transplants per year, and that these units made up more than half the US transplant centres. Davies et al concluded that short- and long-term survival in paediatric heart transplantation was significantly lower in low-volume centres.<sup>14</sup> Worldwide figures<sup>15</sup> as well as single centre studies<sup>16</sup> show a survival of 50% at 10 years (Figure 1). Our unit qualifies as a very low-volume transplant centre and yet our 10-year survival stands at 80%. Several factors may account for this, not least the fact that we do not practice distant retrieval. Moreover patient contact is very thorough and any complication is dealt with expeditiously. Following the two operative deaths from pulmonary hypertension we altered our acceptance criteria for potential recipients to those with a PVR of less than 2.5 Wood units, even if this was achieved after maximal oral vasodilator therapy.

In the patients who developed abdominal complications, presentation was unusual. Thus the patient who developed appendicitis presented with a purulent discharge from a recent groin entry point used for myocardial biopsy. At surgery a gangrenous appendix was removed. Similarly the patient who developed a pelvic abscess secondary to an infected ovarian cyst experienced no abdominal pain and presented with pyrexia of unknown origin. The patient who underwent left hemicolectomy for extensive diverticulitis presented with mild rectal bleeding which increased dramatically over the course of a day. Abdominal complications are a recognised feature in the early post-transplant course. Five to ten percent of transplantees require laparotomy to establish a prompt diagnosis and the procedure is well tolerated.<sup>17,18</sup>

Cytomegalovirus (CMV) infection is the single most important viral infection in heart transplant recipients, and is most prevalent in the first year.<sup>19,20</sup> Two of the four patients who developed CMV infection were sero-negative before transplantation and received a sero-positive heart (D+/R-). Patient 11 presented with severe abdominal pain and patient 12 with headaches. Patients 6 and 13 developed a reactivation infection, both presenting with pyrexia. All patients received intravenous ganciclovir until the polymerase chain reaction (PCR assay) became negative, followed by a nine-week course of oral valganciclovir treatment.<sup>21</sup>

Nephrotoxicity is a well-recognised complication of long-term cyclosporine use. Two of our patients developed a creatinine level of over 300µmol/L and one is on peritoneal dialysis. In our series cyclosporine remained the calcineurin inhibitor of choice because of its proven long-term allograft survival with adequacy of renal function.<sup>22</sup> Reduction in cyclosporine dose is associated with an increased rate of rejection events.<sup>23</sup> Reducing the cyclosporine dose and substituting the azathioprine for mycophenolate<sup>24</sup> may improve renal function. Newer immunosuppressive agents, such as sirolimus and tacrolimus may play a role in this setting.<sup>25</sup>

## Conclusion

Heart transplantation is an effective modality of treatment for certain patients with refractory heart failure. Long-term survival can be achieved in a high proportion of patients. Outcomes are not necessarily related to transplant volume.

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