Current outcome of heart transplantation: a 10-year single centre perspective and review

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Summary

Background: Heart transplantation (HTx), the gold standard therapy for advanced heart failure, is limited by donor availability; alternative therapies are now becoming available.

Aim: We examined the outcome of HTx with current immunosuppressive and adjunctive therapy.

Design and methods: We analysed the outcome of 399 consecutive patients who underwent transplantation at our centre (1995–2007). Prior to HTx 23% (98) required inotropic support, 8.5% (34) an intra-aortic balloon pump and 11% (43) a ventricular assist device.

Results: Actuarial patient survival was 86% at 30 days, 79% at 1 year and 62% at 10 years. Survival was similar regardless of the heart failure severity, \( P = 0.22 \). The cumulative incidence of allograft vasculopathy, Costanzo grade \( \geq 2 \), was 7% at 5 years and 23% by 10 years with an 11% cumulative probability of requiring a percutaneous coronary intervention by 10 years. Allograft function was preserved with a mean \( \pm \) SD left ventricular ejection fraction of 73 \( \pm \) 7% at 1 year and 74 \( \pm \) 8% at 10 years. The cumulative incidence of malignancy by 10 years was 27% (skin malignancy 13% and post transplant lymphoproliferative diseases 10%). The cumulative incidence of developing chronic kidney disease (CKD) with an estimated glomerular filtration rate \( \leq 45 \) ml/min/1.73 m\(^2 \) was 42% at 1 year, 62% at 5 years and 72% at 10 years and of requiring long-term renal replacement therapy was 10.6% at 10 years.

Conclusion: HTx provided good medium-term survival for patients with advanced heart failure, independent of its severity. The incidence of allograft vasculopathy was lower than reported previously but malignancy and CKD remain cause for concern.

Introduction

Advanced heart failure is a serious condition associated with significant morbidity and mortality,1–3 although developments in medical therapy have improved prognosis.4–8 Cardiac resynchronization therapy has shown to improve symptoms, exercise capacity and reduce mortality in patients who have a prolonged QRS duration causing left ventricular dyssynchrony.9,10 Intra-cardiac defibrillators have
also been shown to reduce mortality. However, despite these advances the mortality rate remains high. Implantable ventricular assist devices, as a bridge to cardiac transplantation, may be considered in patients who fail to respond to conventional medical therapy. Heart transplantation (HTx) is an accepted treatment for patients with advanced heart failure. It provides better survival than medical therapy alone.

The first successful human transplant was performed in 1967, but survival rates remained relatively low, until the introduction of ciclosporin (CsA) as an immunosuppressive agent. The International Society for Heart and Lung Transplantation (ISHLT) registry currently reports survival rates of 79% at 1 year, 65% at 5 years and 45% at 10 years. The registry data include a large number of patients; however, it averages the results from different centres in different countries and may lag behind the results being achieved in individual centres. Furthermore, limited information is collected by the registry. Therefore, we studied the outcome of HTx at our centre and have compared it with those reported nationally and internationally as well as historically.

Patients and methods

We analysed 399 patients who underwent HTx at The Royal Brompton and Harefield NHS Foundation Trust, Harefield Hospital, from January 1995 to September 2007. We excluded patients who underwent combined organ transplants (heart–lung, heart–liver or heart–kidney) or heterotopic transplants. Patients’ characteristics are shown in Table 1.

All patients received CsA and corticosteroids with either mycophenolate mofetil (MMF) or azathioprine. Induction therapy with antithymocyte globulin was given to all patients transplanted after 1997.

MMF and azathioprine were maintained unless myelosuppression or other side effects occurred. Corticosteroids were tapered gradually and discontinued by the end of the first transplant year. Patients who experienced either clinical or cellular rejection episodes were treated with high-dose corticosteroids (intravenous methylprednisolone) and further steroid tapering was delayed for ≥3 months.

By protocol, all patients transplanted from August 1999 onwards routinely received a prophylactic 3-hydroxy-3-methylglutaryl-coenzymeA (HMG-CoA) reductase inhibitor, pravastatin 40 mg/day.

The strategy for cytomegalovirus (CMV) prevention changed during the study. All patients initially received acyclovir (1995–99), oral ganciclovir was introduced for primary mismatched patients (donor positive and recipient negative) from February 2002, valganciclovir replaced ganciclovir in 2004. All blood products administered after November 1999 onwards were leucodepleted.

Coronary angiography was performed, by protocol, in the first few weeks after transplantation, at year 1 and then every other year until year 7 and then year 10. Patients who had evidence of cardiac allograft vasculopathy (CAV) underwent addition coronary angiography as required clinically.

<table>
<thead>
<tr>
<th>Table 1 Patient and donor characteristics</th>
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<tr>
<td><strong>Recipient age, mean ± SD (range) (years)</strong></td>
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<tr>
<td><strong>Gender, male, n (%)</strong></td>
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<td><strong>Pre-transplant diagnosis, n (%)</strong></td>
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<tr>
<td>Ischaemic cardiomyopathy</td>
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<td>Dilated cardiomyopathy</td>
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<td>Valvular heart disease</td>
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<td>Other</td>
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<td><strong>Pre-operative NYHA class, n (%)</strong></td>
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<td>Class 3</td>
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<td>Class 4</td>
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<tr>
<td><strong>Pre-transplant left ventricular ejection fraction (mean ± SD) (%)</strong></td>
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<td><strong>Pre-transplant circulatory support, n (%)</strong></td>
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<td>Inotropic support</td>
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<td>Intra-aortic balloon pump</td>
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<td>Ventricular assist device</td>
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<td><strong>Pre-transplant creatinine level, mean ± SD (µmol/l)</strong></td>
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<td><strong>Pre-transplant eGFR median (IQR) (ml/min/1.73 m2)</strong></td>
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<td><strong>Pre-transplant DM, n (%)</strong></td>
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<td><strong>Post-operative acute renal failure, n (%)</strong></td>
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<td><strong>Donor details</strong></td>
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<td><strong>Donor age, mean ± SD (range) (years)</strong></td>
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<td><strong>Male gender, n (%)</strong></td>
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<td><strong>Median total ischaemia time (IQR) min</strong></td>
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<td><strong>Cause of donor death, n (%)</strong></td>
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<td>Cerebrovascular accident</td>
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<tr>
<td>Trauma</td>
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<tr>
<td>Domino heart</td>
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<tr>
<td>Hypoxia</td>
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<tr>
<td>Poisoning</td>
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<tr>
<td>Meningitis</td>
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<tr>
<td>Metabolic (diabetic ketoacidosis)</td>
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<td>Unrecorded</td>
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CAV was classified using the Costanzo grading system (Table 2). Cardiac allograft function was estimated routinely by the global left ventricular ejection fraction on trans-thoracic echocardiography.

Estimated glomerular filtration rate (eGFR) was calculated according to the four-variable formula used in the Modification of Diet in Renal Disease (MDRD) Study. Ethical permission was obtained for the retrospective analysis of data.

**Statistical analysis**

The results are presented as mean ± SD or proportion (percentages) as appropriate. Actuarial graft survival (death or re-transplant), the cumulative incidence of CAV, malignancies and chronic kidney disease (CKD) were calculated using the Kaplan–Meier method, as were the cumulative incidences of percutaneous intervention or need for renal replacement therapy.

**Results**

Patient and donor characteristics are shown in Table 1. Ischaemic heart disease was the indication for HTx in 45% and dilated cardiomyopathy in 45% patients. Thirty-three percent of the patients required some form of pre-transplant circulatory support, 23% inotropic support, 8.5% had an intra-aortic balloon pump and 11% a ventricular assist device. None of the patients were on renal replacement therapy pre-transplant. The main causes of donor death were cerebrovascular accidents and trauma.

**Survival and allograft function**

Actuarial recipient survival was 86% at 30 days, 79% at 1 year, 77% at 3 years, 73% at 5 years and 62% at 10 years, Figure 1. Conditional survival >30 days was 91% at 1 year, 86% at 5 years and 73% at 10 years, while conditional survival >1 year was 97% at 3 years, 93% at 5 years and 79% at 10 years (mean annual mortality rate of only 2.3% between 1 year and 10 years).

There was no difference in survival between patients with ambulatory heart failure and those with decompensated heart failure—New York Heart Association (NYHA) Class 4—receiving inotropic support and intra-aortic balloon pump or ventricular assist device, $P = 0.2$, Figure 2.
The use of ventricular assist devices pre transplant had no influence on survival, 84 vs. 79% at 1 year and 77 vs. 73% at 5 years, $P=0.5$. In addition there was no difference in survival by era (1995–99 vs. 2000–05), $P=0.5$, Figure 3.

Allograft function assessed by trans-thoracic echocardiography was preserved with a mean ± SD left ventricular ejection fraction of 73 ± 7% at 1 year, 75 ± 6 at 5 years and 74 ± 8% at 10 years.

Immunosuppression and acute rejection

Acute treatment consisted of intravenous methylprednisolone combined, with anti-thymocyte globulin. Few patients ($n=69$; 17.3%) were switched from CsA to tacrolimus or sirolimus for repeated rejection 56/69 (81%) or renal dysfunction 13/69 (19%). The mean time to immunosuppression switch was 0.8 ± 1.5 years.

CAV

The cumulative incidence of CAV (Costanzo grades moderate and severe) was 4% at 3 years, 7% at 5 years and 23% at 10 years, while the cumulative incidence of severe CAV was 4.7 and 11% at 5 and 10 years, respectively. The cumulative probability of requiring percutaneous intervention by 5 and 10 years was 4.5 and 11%, respectively, Figure 4.

Two patients in the study had donor-transmitted coronary vascular disease, one requiring coronary artery bypass grafting at the time of transplant and the second patient within the first year following transplantation. Percutaneous coronary intervention was required by 18 patients. No patients underwent coronary artery bypass grafting for long-term acquired CAV.

Causes of death

Less than half (40%; 55/138) of the deaths occurred within the first month after transplantation. Early post-operative death was mainly due to primary allograft dysfunction, 55% (30/55). Two patients died of hyperacute antibody mediated rejection (AMR).

Acute allograft rejection was the cause for 32% (10/31) of deaths after the first month and before the end of the first year. Late death >1 year was most often due to an underlying malignancy 35% (18/52), chronic rejection and CAV 25% (13/52) and AMR 4% (2/52), or acute cellular rejection (ACR) 8% (4/52), Table 3.

Renal function

Pre-transplant median eGFR was 71 ml/min/1.73 m², (IQR 55–80). Twenty-six percent of patients required temporary renal replacement therapy with veno-venous haemofiltration in the early post-operative period. Median eGFR declined to 52 ml/min/1.73 m² (IQR 38–62) at 1 year following transplantation, 50 ml/min/1.73 m² (IQR 35–60) at 5 years and 46 ml/min/1.73 m² (IQR 32–61) at 10 years. The cumulative incidence of developing CKD with an eGFR <45 ml/min/1.73 m² was 42% at 1 year, 62% at 5 years and 72% at 10 years.

By 10th year, 97% (107/110) of the patients had developed a degree of renal impairment with an MDRD eGFR <90 ml/min/1.73 m² (CKD Stage 2). The cumulative probability of requiring long-term renal replacement therapy at 10 years was 10.6%.
Long-term renal replacement therapy for late renal failure was required by 18 patients, 12 were haemodialysed, 3 had peritoneal dialysis and 3 underwent renal transplantation (2 of whom were initially haemodialysed and 1 had a pre-emptive renal transplant).

**Post-transplant malignancy**

The cumulative incidence of developing any malignancy at 1, 3, 5, 7 and 10 years was 4, 7, 12, 18 and 27%. The cumulative incidence of skin malignancy was 2% at 1 year, 4% at 3 years, 6% at 5 years, 8% at 7 years and 13% at 10 years, whereas that of post-transplant lymphoproliferative disease (PTLD) 1, 2, 6, 3, 4, 5 and 10%. No melanomas were reported during this study.

Other malignancies originated from lung (2), colon (2), liver (1), kidney (1), larynx (1), brain (1) and blood (1 myelodysplasia). Two patients had metastatic malignant disease of unknown primary. Thirteen percent (18/138) of deaths were due to a malignancy, of which 5% (7/138) were due to lymphoproliferative disease.

**Infection**

Death from infection mainly occurred within the first year and was primarily bacterial in origin. Three patients died of disseminated or pulmonary aspergillosis, while one patient died of disseminated toxoplasmosis. Throughout the study 6% (56/399) of patients developed a CMV antigenaemia necessitating treatment. There were no deaths from CMV infection.

**Diabetes mellitus**

Twelve percent (47/391) of the patients had pre-transplant diabetes mellitus (DM). Post-transplantation, a further 9.4% (32/342) of patients developed DM.

**Discussion**

Post-transplantation survival (62% at 10 years) exceeded that achieved in previous eras and that currently reported by the UKCTA (56%), the ISHLT (51%) and the Organ Procurement and Transplant Network (OPTN), US scientific registry of Transplant Recipients (SRTR) (56%). Other single centres have reported 10-year survival rates of 19–71%.

Unlike medical therapy, the outcome of HTx was independent of the preoperative severity of heart failure.

The annual late mortality rate in this study (2.3%) was lower than that recorded by both the UKCTA database (2.9%) and the ISHLT (3.4%). It is also lower than that reported in the active arm of most heart failure drug trials, which generally included...
patients with less severe heart failure than those undergoing HTx.\textsuperscript{15}

The early mortality was similar to that generally reported from the UK but higher than that reported in North America.\textsuperscript{27–29} This early mortality rate has not changed with time and the principal cause is primary allograft failure.\textsuperscript{27} This contrast with the ISHLT registry data where early survival has improved with time: and may reflect the relatively high risk-profile of cardiac donors currently available for transplantation in the UK and adverse trends such as increasing donor age and organ ischaemia time.\textsuperscript{34–37}

ACR has become less frequent following the introduction of MMF\textsuperscript{38–39} and routine induction therapy,\textsuperscript{40,41} as well as routine use of statins.\textsuperscript{32,43} As a result, acute rejection has become a less common cause of death after HTx; 15\% in this cohort and 12\% in the ISHLT registry.\textsuperscript{23}

All patients had a retrospective human leukocyte antigen (HLA) cross-match, which was negative except in two cases. Endomyocardial biopsies were not routinely tested for complement deposition and signs of antibody mediated rejection (AMR) and this may have caused a clinical delay in diagnosing AMR. The criteria for diagnosing AMR have evolved during the period covered by this study and therefore AMR maybe underestimated. Although AMR is less common than ACR, it can cause significant allograft dysfunction in both early and late post-transplant periods.\textsuperscript{44–47} However, in this study only 3\% (4/138) of patients died from delayed AMR.

The incidence of angiographically detected CAV (Costanzo grades moderate and severe) was lower compared with that in the 1998 Costanzo report\textsuperscript{25} and the 2009 ISHLT registry.\textsuperscript{23} Furthermore, the proportion of deaths from CAV was low (14/138, 10\%) compared with that reported by the ISHLT registry (32\%).\textsuperscript{23} Only one patient in the study developed accelerated CAV within the first year and he died 18 months following transplantation.

From 2000 onwards all patients were immuno-suppressed with MMF, which has been shown to reduce acute rejection and antibody production as well as intimal thickening.\textsuperscript{38,39,48–52} Rapamycin (sirolimus) has also been used as an adjuvant immunosuppressive agent to replace calcineurin inhibitors (CNIs) in patients with angiographic CAV and stable renal function. In our cohort, 17\% of patients had their immunosuppression switched for acute rejection or CAV. Only six patients (1.5\%) were switched to sirolimus for acquired CAV. The number of patients requiring percutaneous coronary intervention was low and none of the patients had a coronary artery bypass graft surgery for acquired CAV. Thus, it appears that advances in medical therapy with MMF, statins and sirolimus have helped to delay the development and progression of CAV. This used to be the predominant cause of late deaths after HTx\textsuperscript{53} but is no longer the case; nevertheless, CAV remains an important cause of late death.

Malignancy is a serious complication following transplantation that appears to be mainly caused by pharmacological immunosuppression. The cumulative incidence of any malignancy was 27\% at 10 years while that of PTLD was 10\%. This is lower than that reported by the UK registry,\textsuperscript{54} but malignancy was the commonest cause of late death in this cohort (Table 3).

The incidence of CKD increased progressively with time after transplantation.\textsuperscript{55–57} Therefore, this problem is becoming more apparent as long-term survival improves. Here, the cumulative incidence of Stages 2 and 3 diseases was 97\% and 72\%, respectively, by 10 years. This is slightly higher than reported in other cardiac studies and for non-renal organ transplants.\textsuperscript{57–62} A number of factors contributing to CKD after HTx have been identified. CsA has been recognized as an important nephrotoxic factor. Other predictors of CKD include post-operative acute renal failure, DM and increasing recipient age.\textsuperscript{63} Although CKD was mostly asymptomatic, some patients went on to end-stage disease requiring long-term dialysis or renal transplantation. Here, the cumulative need for renal replacement therapy was 10.6\% at 10 years. Renal replacement therapy was lower than that reported in other studies; Lubitz et al.\textsuperscript{64} reported a cumulative probability of end-stage renal disease (ESRD) of 4.5\% at 5 years, 19.6\% at 10 years and 44.6\% at 15 years following HTx, while ISHLT reported a 27\% cumulative probability of developing severe renal dysfunction [creatinine >2.5 mg/dl (~220 \mu mol/l), dialysis or renal transplant] by 5 years, 34\% by 7 years and 42\% by 10 years.\textsuperscript{23} In this study, nine patients died from renal failure or its complication.

CMV infection is the most common opportunistic infection following transplantation. However, only 6\% of patients developed CMV antigenaemia necessitating treatment. This probably reflects prophylaxis with acyclovir, ganciclovir and valganciclovir.\textsuperscript{65,66} There were no deaths related to CMV and only four deaths related to other opportunistic infections. However, conventional bacterial infections caused 14\% (19/138) of deaths.

Post-transplant DM is related to CNI and corticosteroid treatment as well as that which occurs naturally with increasing age. The majority of patients gain weight following transplantation, which may also contribute to the development of DM. In this study, 9\% of patients developed non-insulin
dependent DM after transplantation. This is lower than that reported by the ISHLT registry (20%).
We speculate that this may be due at least partly to the fact that we actively weaned patients from corticosteroid therapy, 49% of patients were weaned off by the end of the first year and 78% by 3 years, which is higher than the 2009 ISHLT registry that reports only 21% of patients off corticosteroid by the first year and 46% by 5 years, whereas the SRTR registry reports 33% by 1 year.

**Study limitations**
This was an observational cohort study. Cardiac allograft function was mainly evaluated by echocardiographic left ventricular ejection fraction. The incidence of CAV may be an underestimate because this was assessed by coronary angiography and not by intra-vascular ultrasound; however, the incidence in earlier eras, as discussed above, was also based on angiography. The patients were not routinely screened for AMR during the period covered by study. The incidence of skin malignancies may also have been underestimated as minor lesions that were treated locally may not have always been recorded.

**Conclusion**
The medium-term survival following HTx for advanced heart failure was good and much better than that which could have been achieved by medical therapy alone; hence HTx remains the standard-of-care for selected patients with advanced heart failure. The results of HTx are the current benchmark against which to compare other treatments. However, transplant activity is now limited by the availability of suitable donor hearts and newer heart failure therapies are becoming available such as mechanical circulatory assist devices. Medium-term survival after HTx remains better than that currently achieved with mechanical circulatory support using a left ventricular assist device (LVAD) (77 vs. 58% at 2 years, respectively). Therefore, it is still rational to consider LVAD support as principally a bridge to transplantation, rather than as a long-term treatment, for patients who are eligible for transplantation.

Nevertheless, LVAD support provides an alternative treatment for patients who are either unsuitable for transplantation or are unable to undergo transplantation in a timely fashion because of the lack of a suitable donor heart.

The improved long-term results of HTx appear to be due to a reduction in the number of deaths from acute rejection and CAV. In contrast, little progress has been made with the prevention and management of primary allograft failure or malignancy. Primary allograft dysfunction remains the major cause of early postoperative deaths. There needs to be further research into donor management and particularly myocardial protection during the period between cardiac retrieval and implantation. The incidence of late death from malignancy remains a cause for concern and is now an important factor limiting long-term survival as in other forms of organ transplantation. In the future, improved screening methods may facilitate earlier diagnosis and so reduce deaths from this cause. Morbidity from CKD and the eventual need for secondary renal transplantation is another important issue. Non CNI-based immunosuppression may help to reduce this problem, but the efficacy and safety of such regimens remain to be established.

**Conflict of interest:** None declared.

**References**