Ten year survival after heart transplantation: palliative procedure or successful long term treatment?

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Abstract

Objective—To investigate the long term outcome and prognostic factors after heart transplantation.

Setting—University hospital.

Subjects—120 heart transplant patients (98 male, 22 female; underlying disease: dilated cardiomyopathy in 69, coronary artery disease in 42, miscellaneous in nine) who had undergone heart transplantation between October 1984 and October 1987. Immunosuppressive treatment was comparable in all patients and rejection episodes were treated in a uniform manner.

Methods—Functional status, quality of life, and potential predictors for long term survival were investigated.

Results—Actuarial survival rates were 65% at five years and 48% at 10 years; 58 patients survived > 10 years. The major causes of death were cardiac allograft vasculopathy (39%), acute rejection (18%), infection (11%), and malignancy (11%). Long term survivors had good exercise tolerance assessed by the New York Heart Association classification: 47 (81%) in grade I/II; 11 (19%) in grade III/IV. Echocardiography showed good left ventricular function in 48 patients. On angiography, severe allograft vasculopathy was present in only 16 patients (28%). Renal function was only slightly impaired, with mean (SD) serum creatinine of 148.5 (84.9) µmol/l. Multiple potential predictors of long term survival were analysed but none was found useful.

Conclusions—Heart transplantation represents a valuable form of treatment. Survival for more than 10 years with a good exercise tolerance and acceptable side effects from immunosuppression can be achieved in about 50% of patients.

Keywords: heart transplantation; long term survival

Despite recent progress in the conservative treatment of symptomatic heart failure, the clinical course of this disease remains dismal. The introduction of vasodilators and angiotensin converting enzyme (ACE) inhibitors has improved the outcome significantly but mortality remains high. A six month mortality of between 20% and 30%, as shown in the CONSENSUS (cooperative north Scandinavia-
Table 1  Patient characteristics and evaluation of potential predictors for long term survival

<table>
<thead>
<tr>
<th>Factors</th>
<th>All patients (n = 120)</th>
<th>Long term survivors (n = 58)</th>
<th>Deceased patients (n = 62)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recipient related factors</strong></td>
<td></td>
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<td></td>
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<tr>
<td>Age at transplant (years)</td>
<td>42.3 (11.8)</td>
<td>42.1 (11.5)</td>
<td>42.5 (11.6)</td>
<td>0.8</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Male</td>
<td>98 (81.7%)</td>
<td>94 (82.1%)</td>
<td>44 (71%)</td>
<td>0.4</td>
</tr>
<tr>
<td>Female</td>
<td>22 (18.3%)</td>
<td>9 (15.5%)</td>
<td>13 (21%)</td>
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<tr>
<td>Cause of heart failure</td>
<td></td>
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<tr>
<td>DCM</td>
<td>69 (57.5%)</td>
<td>36 (62.1%)</td>
<td>33 (53.2%)</td>
<td>0.2</td>
</tr>
<tr>
<td>CAD</td>
<td>42 (35%)</td>
<td>16 (27.6%)</td>
<td>26 (41.9%)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>9 (7%)</td>
<td>6 (10.3%)</td>
<td>3 (4.8%)</td>
<td></td>
</tr>
<tr>
<td>Cholesterol at year 1 (mmol/l)</td>
<td>6.7 (2.0)</td>
<td>7.0 (2.3)</td>
<td>6.4 (1.6)</td>
<td>0.1</td>
</tr>
<tr>
<td>Triglycerides at year 1 (mmol/l)</td>
<td>2.6 (1.8)</td>
<td>2.6 (1.9)</td>
<td>2.5 (1.4)</td>
<td>0.8</td>
</tr>
<tr>
<td><strong>Drug treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean dose of azathioprine (mg/day)</td>
<td>99.8 (30.4)</td>
<td>102 (25.5)</td>
<td>97 (35.2)</td>
<td>0.3</td>
</tr>
<tr>
<td>Mean dose of cyclosporin (mg/day)</td>
<td>327.8 (83.0)</td>
<td>318.7 (81.8)</td>
<td>338.1 (84.0)</td>
<td>0.2</td>
</tr>
<tr>
<td>ATG treatment</td>
<td>99</td>
<td>46</td>
<td>53</td>
<td>0.7</td>
</tr>
<tr>
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<td>97 (35.2)</td>
<td>0.4</td>
</tr>
<tr>
<td>Mean dose of prednisolone at year 1 (mg/day)</td>
<td>10.9 (3.4)</td>
<td>10.7 (3.7)</td>
<td>10.9 (3.0)</td>
<td>0.8</td>
</tr>
<tr>
<td>Number of antihypertensive drugs at year 1</td>
<td>1.2 (0.9)</td>
<td>1.0 (0.9)</td>
<td></td>
<td>0.7</td>
</tr>
</tbody>
</table>

Data are expressed as mean value (SD) and n (%). Groups were compared by unpaired two tailed t test for independent values. Non-continuous variables were assessed by χ² analysis. p Values < 0.05 were considered statistically significant.

ATG, antithymocyte globulin; CAD, coronary artery disease; DCM, dilated cardiomyopathy.

Data analysis was performed using a computer assisted software package (SPSS, version 6.0.1). Continuous variables are presented as mean (SD). Univariate comparison between surviving and deceased patients for different risk factors was performed by χ² test for non-continuous variables and by unpaired two tailed t test for continuous values. For multi-variate analysis, a logistic regression was chosen (backward, LR). Probability (p) values < 0.05 were considered significant. Actuarial survival rates were computed according to the Kaplan–Meier estimate using the log rank test.

RESULTS

SURVIVAL

Of the total cohort, 58 patients survived more than 10 years, with an actuarial survival rate of 78.3% at 1 year, 65% at 5 years, and 48% at 10 years (fig 1).

There were 62 deaths among the study population during the follow up period. Causes of death in the entire study group are given in fig 2A. The most common causes of death were chronic graft failure owing to CAVD (n = 24; 39%), early right heart failure (n = 11; 18%), infections (n = 7; 11.2%), and malignancies (n = 7; 11.2%). Forty per cent of the deaths occurred within the first year of transplantation, mainly from acute graft rejection. Causes of death in year 1 are shown in fig 2B.

GRAFT FUNCTION AND SIDE EFFECTS OF IMMUNOSUPPRESSION

In the study population, 58 patients (48.3%) survived the 10 year period, with a mean observation period of 11.1 (0.7) years. Assessment of the quality of life by the self assessment questionnaire was optimistic in about 75% of the patients. Only two patients were seriously dissatisfied. To the question “Would you decide to have a heart transplant again?” only five gave a negative response. Exercise toler-
ance in long term survivors could be shown to be excellent, with 14 patients (24.1%) being in New York Heart Association (NYHA) functional class I, 33 (56.9%) in class II, nine (15.5%) in class III, and two (3.4%) in class IV, as assessed by routine visits to the outpatient department. Normal graft function was demonstrated by echocardiographic quantification of left ventricular contractility, with a mean (SD) ejection fraction of 61 (5)%.

As an index of end organ impairment we assessed renal function, defined by serum creatinine. The mean serum creatinine was 148.5 (84.9) µmol/l, showing an acceptable functional status, with only one patient requiring chronic haemodialysis. Table 2 gives the data for this group.

ALLOGRAFT VASCULOPATHY
The most recent coronary angiography in the survivors showed no signs of graft vasculopathy in 27 patients (46.6%), 15 (25.8%) had a luminal obstruction of grade 1 or 2, and only 16 (27.6%) had high grade vasculopathy. Coronary angiograms were available in 31 deceased patients; in 13 cases (41.9%) a luminal obstruction of 50% and more was detectable, as compared with 16/58 (27.6%) in long term survivors. In addition, the latency until the first sign of graft vasculopathy (< 30% luminal obstruction) diagnosed in this group was 40.9 (31.6) months, whereas the latency in the long term surviving group was 76.4 (28.5) months.

MALIGNANCY
There was a high incidence of malignant tumours in both the deceased patients and the long term survivors. In the overall cohort, 17 patients (14.1%) developed non-cutaneous malignant tumours, with lymphoma being the commonest (nine cases, 52.9% of all tumours). Malignancy was the cause of death in 11% of the deceased patients. However, malignant disease was found in the long term survivors as well (eight cases (13.7%): lymphoma in three, lung cancer in two, colon cancer in one, and haematological neoplasia in one), five of these being in complete remission after successful treatment at the time of writing.

ANALYSIS OF PREDICTIVE FACTORS
Analysis of predictive factors was performed comparing characteristics of the long term survivors and the deceased patients. Using both a univariate analysis and a multivariate logistic regression, no independent predictors of long term survival for more than 10 years could be identified. The data on factors relating to recipient, donor, procedure, and treatment are summarised in table 1. There was no significant difference between the two groups. There was a trend for a higher proportion of patients with dilated cardiomyopathy to survive more than 10 years after heart transplantation; this resulted in a 10 year survival rate of 38% for coronary artery disease versus 55% for dilated cardiomyopathy (NS, log rank test).

Discussion
During the past 25 years considerable progress has been made in understanding the pathogenesis of the heart failure syndrome. On the basis of this knowledge several advances have been made in the conservative management in this patient group. However, despite the introduction of vasodilators and ACE inhibitors, one year mortality still ranges from 15% among unselected patients to 50% among those in NYHA functional class IV. In contrast, heart transplantation allows one year and five year survival rates of about 80% and 60% to 70%, respectively. However, with more than 30 years of clinical experience with replacement of the heart, only limited data are
available in allograft recipients surviving 10 years and more. We therefore analysed a patient population undergoing heart transplantation more than 10 years earlier to characterise survival, graft function, and side effects of immunosuppression in the hope of identifying potential predictors of long term survival.

Our study represents a single centre approach with a 10 year survival rate of 48%, compared with 45% reported by the multicentre International Society for Heart and Lung Transplantation registry. These results are far superior to medical treatment alone. Before the introduction of vasodilators and ACE inhibitors, a one year mortality of approximately 50% was the norm with conservative management. In the CONSENSUS trial, in which patients with severe heart failure were randomised to receive placebo or enalapril in addition to conventional treatment, the mortality at 12 months was 36% in the enalapril group and 52% in the placebo group.6 In the V-Heft I (vasodilator in heart failure) study, which included patients with mild to moderate clinical heart failure, the cumulative mortality over four years was 53.6%.

However, quality of life is also a major issue after heart transplantation. In the CONSENSUS study, 42% of the enalapril treated patients had improvement in their NYHA functional class, but three quarters of the surviving patients remained in NYHA functional class III and IV. In our transplant population the majority of patients (81%) were in NYHA functional class I and II as long as 10 years after the procedure. Exercise tolerance proved to be remarkably improved compared with optimum medical treatment. Furthermore, invasive and non-invasive evaluation of graft function by cardiac catheterisation and echocardiography revealed normal cardiac function with a mean ejection fraction of 61 (5%). These results are in agreement with the findings of previous investigations.13–14 In 1993, von Scheidt evaluated the long term haemodynamic profile of heart transplant recipients up to seven years after the procedure and reported essentially normal systolic function with no evidence of the development of a dilated or restrictive post-transplantation cardiomyopathy over time.15

Apart from good functional graft status, accelerated graft vasculopathy was identified as one of the most critical issues in the long term follow up of heart transplant recipients.16–18 This unique form of an accelerated coronary syndrome is characterised by endothelial dysfunction and a multifocal intimal hyperplasia modified by coronary artery remodelling.19–21 The prevalence of this complication—as assessed by angiography—is approximately 10% to 15% at one year and 35% to 50% five years after transplantation.22–25 Recent reports were also able to show positive effects on the development of CAVD by lipid lowering treatment with statins as well as by diltiazem administration.26 Because of the retrospective design of our study, comprising patients transplanted between 1984 and 1987, only a small minority received these agents. Future prospective studies will have to evaluate whether the introduction of these drugs (in 1994/95) has resulted in clinical benefit.

The clinical impact of CAVD on heart transplantation was confirmed in our patient cohort. CAVD was the major cause of death in 39% of the patients. In deceased patients the first signs of CAVD (30% luminal obstruction) were diagnosed significantly earlier than in long term survivors (after 40.9 (31.6) months vs 76.4 (28.5) months, p < 0.05). Peak incidence of death from CAVD was between five and 10 years after heart transplantation. Most interestingly, the majority of long term survivors presented with only low grade vasculopathy (72.4% less than grade 2), suggesting a positive selection in this subgroup and raising hopes for a stable subsequent course.

Renal function in our cohort showed only moderate impairment, with a mean serum creatinine of 148.5 (84.9) µmol/l and only one patient requiring chronic haemodialysis. This important finding suggests that chronic damage to the kidneys caused by long term treatment with cyclosporin A can be minimised by optimal adjustment of the dose, using toxicity adjusted drug level monitoring. As shown by Hausen et al, the concept of cyclosporin A dose adjustment governed primarily by renal function does not affect the incidence of rejection.26

Finally, the development of malignancy remains a point of major concern as an important cause of death in long term survivors after any type of solid organ transplantation, as well as in heart transplantation.27–29 Nearly 25% of our patients suffered from malignant disease during the 10 year period (13.7% of long term survivors and 11.2% dying from malignancy). This represents one of the most challenging problems for future attempts to optimise the immunosuppressive protocols. Induction treatment with OKT 3, a major determinant of lymphoma incidence, was not used in our cohort during the study period. ATG was used as cytolytic induction treatment in 99 patients, with no significant difference between survivors and non-survivors.

Searching for predictive factors for survival, Bourge et al reviewed the data from the cardiac transplant research database established in 1990.30 Analysing short term periods, they identified different recipient (younger and older age), donor (older age, smaller body surface area), and clinical (longer ischaemic time) risk factors for death after transplantation. However, evaluation of different recipient, donor, and treatment related factors in our cohort showed no significant influence on long term outcome. The incidence of HLA mismatch, which was shown to correlate with early allograft rejection incidence and graft survival by De Mattos et al and Smith et al,31 was not different in our survivor and non-survivor groups, though complete data were only available in 73% of the patients. Worsnop found a positive trend in patients with dilated cardiomyopathy as the underlying disease, which might reflect the younger age of the recipients (39.1 (12.2) v
48.2 (5.8) years), less concomitant disease, and better general physical condition in this subgroup.

In summary, the results of cardiac transplantation have improved significantly over the last two decades, with an increasing number of patients surviving between 10 and 20 years after transplantation. As we were able to show in our population, nearly 50% of patients will survive a 10 year period with acceptable exercise tolerance and quality of life. Thus heart transplantation should be regarded as a valuable treatment option. The major obstacle for the future of these patients will be to overcome chronic graft vasculopathy and the development of malignancies.

30 De Mattos AM, Head MA, Everett J, et al. HLA-DR matching correlates with early cardiac allograft rejection, incidence, and graft survival when high confidence level serological DR typing is used. Transplantation 1994;54:626–30.