Outcomes in patients with low left ventricular ejection fraction after heart transplantation

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Received 27 September 2002; received in revised form 5 February 2003; accepted 6 February 2003

Abstract

Objectives: Low left ventricular ejection fraction (EF) after heart transplantation (HT) is considered an ominous sign. We reviewed our database in order to determine outcomes in patients with low EF after HT and to identify a subset of patients who would benefit from immediate retransplantation.

Methods: We identified 825 patients who underwent HT at our institution between December 1983 and July 1999. Of these, 81 patients (70 men, 11 women; age, 48 ± 12 years) had low (<35%) EF as determined by radionuclide ventriculography. Post-transplantation survival; duration of low-EF episodes (>2 years vs. <2 years); and incidence of transplant rejection, infection, and transplant coronary artery disease (CAD) were determined for these patients.

Results: On average, low EF developed 800 ± 1029 days after HT and lasted 550 ± 756 days until improvement, repeat HT, or death of the patient. Actuarial survival was 79% at 1 year, 55% at 3 years, and 46% at 5 years. Shorter (<2-year) episodes of low EF tended to have an earlier onset than prolonged (>2-year) episodes (656 days vs. 1341 days) (P = 0.014). Patients with prolonged episodes (n = 17) survived longer than patients with shorter episodes (n = 64) (2247 days vs. 1266 days) (P = 0.002). The incidence of hemodynamically significant rejection was lower in the prolonged low-EF group (6% [1/17] vs. 26% [17/64]) (P = 0.03). The incidence of infection (31% vs. 53%) and incidence of transplant CAD (47% vs. 39%) did not differ significantly between the prolonged and shorter low-EF groups.

Conclusions: Low EF after HT, especially with later onset, is not associated with poor survival and is not related to hemodynamically significant rejection. These data further indicate that the presence of low EF even in the setting of CAD is not by itself an indication for repeat HT.

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Keywords: Heart transplantation; Ejection fraction; Graft rejection; Survival

1. Introduction

Left ventricular ejection fraction (EF) has gained widespread acceptance as a measure of left ventricular systolic function in various clinical settings. However, data on EF after cardiac transplantation are relatively scarce and variably positive and negative. Some studies have shown the EF of cardiac allografts to be comparable to the EF of normal controls up to 4 years after transplantation [1], while others have demonstrated a significant decline in EF during both the short-term [2] and long-term [3] post-transplantation course. This suggests that left ventricular systolic performance after cardiac transplantation varies consider-ably, with EF values lying above and below the cutoff point that is considered normal for the non-transplant population. The prognostic significance of this variation is uncertain: an echocardiographic EF of less than 60% has been shown to be an independent predictor of cardiac events in transplant recipients [4], and a low (<40%) EF as assessed with radionuclide ventriculography at 12 months after transplantation has been associated with an increased cardiac mortality thereafter. However, no association between the decline in EF within the first post-transplantation year and increased late all-cause and cardiac mortality was found [2]. Therefore, the range and prognostic value of low EF after cardiac transplantation remains poorly defined. The aim of our study was to investigate the characteristics and outcome of cardiac transplant recipients in whom EF was low at any time during the post-transplantation course.
2. Materials and methods

2.1. Study population

Eight hundred and twenty-five patients underwent cardiac transplantation at the Texas Heart Institute (THI) between December 1983 and July 1999. We identified 81 adult patients (age ≥ 20 years) who had low EF (< 35%) at any time during the post-transplantation course. The remaining 744 patients were included in the control group. Left ventricular ejection fraction was measured using radionuclide ventriculography. Patients received double-drug maintenance immunosuppression therapy with cyclosporine and prednisone before 1987; after 1987, all patients received triple-drug immunosuppression therapy with cyclosporine, prednisone, and either azathioprine or mycophenolate mofetil.

2.2. Rejection

Endomyocardial biopsies were performed according to a conventional schedule [5]. Additional elective biopsies were performed when rejection was suspected on clinical grounds. Myocardial samples were graded for the presence of rejection using the THI scale of 0–10. A rejection episode was defined as two consecutive biopsy scores of 5 or more on the THI scale. Acute rejection episodes were treated with intravenous methylprednisolone, OKT3, or antithymocyte globulin depending on the severity of the rejection episode, the clinical course of rejection, the hemodynamic compromise, or all three.

2.3. Infection

An infectious episode was defined as the occurrence of an infection requiring at least 1 week of intravenous antibiotic therapy.

2.4. Transplant coronary artery disease

Once a year, all patients underwent coronary angiography, the first procedure being performed 1 year after transplantation. Transplant coronary artery disease was defined as at least one stenotic lesion seen on any of the coronary angiograms.

2.5. Follow-up

Patients were seen weekly at the outpatient clinic for the first several weeks after discharge and at least once every 3 months thereafter. A low-EF episode was defined as starting at the time of the first documented post-transplantation EF < 35% and ending at the time of the first documented improvement to EF > 35%, repeat transplantation, or death.

2.6. Statistical analysis

Statistical analysis was performed with the SAS system (SAS Institute, Inc., Cary, North Carolina). A two-tailed, unpaired Student’s t-test was used to compare the mean values of patients with short (< 2-year) versus prolonged (> 2-year) low-EF episodes. Chi-square analysis was used to compare the groups’ categorical (discontinuous) data. A P value of < 0.05 was considered significant.

3. Results

3.1. Donor and recipient characteristics

Donor and recipient characteristics for patients with low EF were comparable to those for patients in the control group (Table 1). Furthermore, the two groups did not differ in terms of immunosuppression strategies used (Table 2).

3.2. Post-transplantation clinical course

Data on the post-transplantation clinical course of patients with low EF vs. controls are presented in Table 2. The two groups had comparable rejection incidence, infection incidence, transplant coronary artery disease incidence, and renal function.

3.3. Survival after transplantation

The actuarial post-transplantation survival is displayed in Fig. 1. The post-transplantation survival rates at 1 year were 79% in the low-EF group vs. 80% in the controls (P = 0.86). Similarly, no difference in actuarial survival was found at 3 years (55% in the low-EF group vs. 66% in

### Table 1

<table>
<thead>
<tr>
<th>Donor and recipient characteristics for patients with low (&lt;35%) vs. normal (&gt;35%) left ventricular ejection fraction after cardiac transplantation*</th>
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<td>All (n = 825)</td>
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* Data are presented as mean ± SD or number (%). EF, left ventricular ejection fraction; CMV, cytomegalovirus.
controls, \( P = 0.11 \), and at 5 years after transplantation (46% in the low-EF group vs. 61% in controls, \( P = 0.17 \)).

Mean survival of low-EF patients with transplant coronary artery disease was similar to the survival of low-EF patients without transplant coronary artery disease (1686 days vs. 1312 days) \( (P = \text{NS}) \).

### 3.4. Duration of low EF

In 17 patients (21%), the low-EF episode lasted for more than 2 years (mean: 1746 ± 865 days, range: 808–4059 days). In the remaining 64 patients (79%), the low-EF episode was shorter than 2 years (mean: 232 ± 216 days, range: 216–733 days). The shorter low-EF episodes tended to occur earlier after transplantation (mean: 656 ± 925 days, range: 3–3707 days) than did the longer episodes (mean: 1341 ± 1239 days, range: 9–3658 days) \( (P = 0.014) \). The incidence of rejection was lower in patients with prolonged low-EF episodes \( (P = 0.03) \), whereas no difference in the incidence of infection or transplant coronary artery disease was found between the short and prolonged low-EF groups (Fig. 2). On average, patients with prolonged low-EF episodes survived longer after transplantation than did patients with short episodes (2247 ± 1161 days vs. 1266 ± 1146 days) \( (P = 0.002) \). Overall, low EF improved in 48 of 81 (59%) patients. The incidence of EF improvement was comparable in both the short low-EF group (39 patients; 61%) and the prolonged low-EF group (9 patients; 53%) \( (P = 0.55) \).

### 4. Discussion

The principal finding of our study is that low EF (<35%) in cardiac allografts after transplantation is not associated with poor survival. Even in the presence of coexisting transplant coronary artery disease, the survival rates of transplant recipients with low allograft EF are comparable to the survival of patients without low EF and to overall survival rates of patients after cardiac transplantation.

According to data from the International Society for Heart and Lung Transplantation Registry, the overall 1-year survival after cardiac transplantation was 74% between 1980 and 1986 and 85% between 1996 and 1999 [6]. In our study, 79% of patients with a low allograft EF, and 80% of patients with prolonged low-EF episodes survived longer than did patients with short episodes (2247 ± 1161 days vs. 1266 ± 1146 days) \( (P = 0.002) \). Overall, low EF improved in 48 of 81 (59%) patients. The incidence of EF improvement was comparable in both the short low-EF group (39 patients; 61%) and the prolonged low-EF group (9 patients; 53%) \( (P = 0.55) \).
patients without a low EF, survived at least 1 year after transplantation. Since our study cohort included all transplant recipients from 1983 to 1999, the observed survival rates are comparable to the expected overall post-transplantation survival. The cardiac mortality rate of transplant recipients with an allograft EF <40% at 1 year has been shown to be three times higher than the mortality rate of recipients with EF >40% [2], but no data on the prognostic significance of low EF after the 1st post-transplantation year have been reported so far. On average, the low EF in our cohort occurred after the 2nd post-transplantation year and lasted for 1.5 years, the survival of these patients being comparable to the survival of controls and to the expected mean survival of cardiac transplant recipients in general. Although the rate of low EF improvement in our study was comparable in both short and prolonged low-EF groups, the patients with prolonged low-EF episodes survived longer than did the patients with short low-EF episodes. Therefore, even though the significance of low EF may vary at specific time points after cardiac transplantation, the overall presence of low EF in cardiac allografts after transplantation does not seem to alter the survival rates of cardiac transplant recipients.

Cardiac allograft vasculopathy is a major cause of graft failure and death in patients surviving more than 1 year after transplantation [7]. The prevalence of cardiac allograft vasculopathy in our study is comparable to the expected prevalence of angiographically detectable coronary artery disease within the first 5 years after transplantation [8,9]. Furthermore, cardiac allograft vasculopathy was not associated with the duration of low-EF episodes, and the mean actuarial survival was comparable in patients with and without coronary artery disease. Even though endothelium-independent microvascular dysfunction has been implicated as a cause of the deterioration of left ventricular systolic function after transplantation, no association between low EF and vasculopathy of the epicardial arteries has been found [10]. On the basis of these findings, we suggest that factors other than coronary artery disease are important in determining the etiology and prognostic significance of low EF after cardiac transplantation.

In our study, the incidence of rejection episodes in the low-EF group was comparable to that in the control group. However, within the low-EF group, the incidence of rejection episodes was higher in patients whose low-EF episodes were short (i.e., lasted less than 2 years). Since the low EF in these patients tended to occur earlier than in the remaining low-EF patients, the observed increase in rejection incidence in this group may be related to the time course of post-transplantation rejections, which in general occur within the 1st year after transplantation. However, left ventricular systolic function does not change significantly during acute rejection [11], and the number and severity of acute rejection episodes in the 1st year after transplantation has been shown not to influence the long-term course of left ventricular systolic function [12]. The lack of association between rejection incidence and low EF in our study further confirms these findings.

Infectious complications are a major cause of morbidity and mortality after cardiac transplantation, and they particularly affect late post-transplantation mortality. The incidence of infectious episodes in patients with low EF in our study was comparable to that in the control group and below the mean incidence expected for the general post-transplantation population [13], and the presence of infection did not seem to affect the duration of low-EF episodes. Therefore, we failed to document any correlation between infectious complications and low EF in cardiac transplant recipients.

In conclusion, our data indicate that the presence of low EF (<35%) in allografts after cardiac transplantation is not associated with poor survival and is not related to hemodynamically significant rejection. These data further indicate that the presence of low EF even in a setting of coronary artery disease is not by itself an indication for repeat transplantation.

References

