Survival of patients removed from the heart transplant waiting list

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Objective: End-stage heart failure has been associated with high mortality in the absence of transplantation. We evaluated the outcome of patients receiving optimal medical therapy who were removed from the cardiac transplant waiting list to determine survival and predictors of mortality.

Methods: We performed a retrospective review of 27 patients removed from the cardiac transplant waiting list from 1999 to 2001 at our institution.

Results: Mean age was 53 ± 11 years; 16 of the patients were male. Status was IB in 3 cases and II in 24. Median time on the list was 32 months, and median follow-up was 2.9 years. Patients were removed from the transplant list because of either clinical improvement (group A, $n = 18$) or deterioration (group B, $n = 9$). In group A, 13 patients had improved functional status and 10 were in New York Heart Association class 1 or 2; 16 had improved echocardiographic left ventricular function. Survivals at 3 years were 100% in group A and 44% in group B ($P < .01$).

Conclusion: Patients with end-stage heart failure who have clinical response to medical therapy have excellent 3-year survival. These data suggest the necessity of close evaluation of patients waiting for transplantation, with a low threshold for inactivation if persistent clinical improvement is observed.

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Patients with end-stage heart failure continue to have a poor prognosis.¹⁻² Cardiac transplantation has been shown to have a greater survival benefit than conventional medical treatment, as well as the possibility of return to preillness activity levels.³ This observation is less clear-cut with recent advances in multimodal therapy, which have been associated with dramatic improvements in the end points of mortality and hospital admissions.^{4,5} A study stratifying patients according to Heart Failure Survival Score showed that only those at highest risk of dying had a mortality risk reduction with transplantation.⁶ Other observational studies have concluded that candidates surviving longer than 6 months on the waiting list should be considered too well for transplantation.^{7,8}

TABLE 1. Clinical status of group B patients

Progressive renal dysfunction
Refused transplant due to age
Peripheral vascular disease
Worsening chronic obstructive pulmonary disease
Obesity with dietary noncompliance
Age-related renal dysfunction
Pulmonary hypertension
Renal insufficiency with pulmonary hypertension
Renal insufficiency with cerebrovascular accident

There is growing consensus that each patient's clinical status and need for transplantation should be reassessed periodically. However, there are no data available on the short- and long-term survivals of patients who have been removed from the United Network for Organ Sharing (UNOS) registry. We sought to evaluate the outcomes of these patients to determine overall survival and predictors of mortality.

Methods

The study was a retrospective review of the clinical records of patients who were removed from the heart transplant waiting list between August 1, 1999, and July 31, 2001. Patients were initially registered between September 1993 and November 2000. Data from the transplant database were supplemented from the clinical files of each patient. In the case of missing variables, inpatient medical records were reviewed. The study was approved by the institutional review board of the Washington University School of Medicine.

Clinically relevant variables included age, sex, diagnosis, listing status at time of registration, and reason for transplant list inactivation. New York Heart Association (NYHA) functional class and left ventricular function as assessed by echocardiography were noted both at listing and at inactivation. Current cardiovascular medications were recorded, as was any use of inotropic therapy or surgical intervention such as pacemaker or automatic implantable cardiac defibrillator (AICD). Patients' treatment regimens were based on published guidelines of tailored optimal medical therapy.^{9,10}

Patients were followed up until August 1, 2002. Information regarding survival or the circumstances of death was obtained from the chart review or from the referring physician assigned to the patient's care. No patients were unavailable for follow-up.

All data were entered into an Excel spreadsheet (Microsoft Corporation, Redmond, Wash). Differences between population subgroups were analyzed by Pearson χ^2 test for nominal variables. Kaplan-Meier survival curves were constructed from the patient cohort and for specific combinations of dichotomous characteristics. Statistical analysis and Kaplan-Meier survival curves were calculated with SYSTAT software (Systat Software, Inc, Point Richmond, Calif).

Results

A total of 27 patients included in this study were divided into two groups. Group A (n = 18) consisted of patients

TABLE 2. Clinical characteristics at listing

Characteristic	Group A (n = 18)	Group B (n = 9)	P value
Age (y, mean $\pm$ SD)	48.7 $\pm$ 10	61.4 $\pm$ 6	<.01
Sex (male/female ratio)	8:10	8:1	.04
Cause of heart failure (No.)			.07
Idiopathic	15	4	
Ischemic	3	5	
Listing status (No.)			.25
IB	1	2	
II	17	7	
NYHA class (mean $\pm$ SD)	3.17 $\pm$ 0.7	3.44 $\pm$ 0.7	.26
Left ventricular function by echocardiography* (mean $\pm$ SD)	3.89 $\pm$ 0.3	3.89 $\pm$ 0.3	>.99
Inotropic support (No.)	1	2	.25
Permanent pacemaker (No.)	1	1	.60
AICD (No.)	6	4	.57

*Left ventricular function classified as follows: 1, Normal; 2, mild dysfunction; 3, moderate dysfunction; 4, severe dysfunction.

whose removal code in the UNOS registry, as determined by the evaluating cardiologist, was classified as clinical improvement with medical therapy. Group B (n = 9) consisted of patients who were removed because of advancing age (n = 2) or clinical deterioration (n = 7), making them unsuitable candidates for transplantation (Table 1).

With respect to clinical characteristics, group B patients were older, more likely to be male, and likely to have ischemic cardiomyopathy (Table 2). There was no difference in functional status according to NYHA class or left ventricular function by echocardiography at listing.

At the time of removal from the waiting list, 13 group A patients (72%) had improved NYHA functional status, and 10 (55%) were in NYHA functional class I or II (mean class 2.28 $\pm$ 0.8). Echocardiographic left ventricular function improved in 16 patients (88%, mean 2.56 $\pm$ 0.8). Altogether, all 18 group A patients showed improvement: 2 by NYHA functional status only, 5 by echocardiography, and 11 by both. Among group B patients, only 3 (33%) had improvement in NYHA functional class, and 2 (22%) had deterioration (mean class 3.33 $\pm$ 0.5). There were no changes in left ventricular function in this group.

Of all patients, 85% were receiving angiotensin converting enzyme inhibitors, 89% were receiving digoxin, and 93% were receiving furosemide. There was no difference in medical treatment between the two patient cohorts. In addition, 3 patients were in status IB with a need for inotropic therapy, 2 patients had implanted pacemakers, and 10 had AICDs.

During the follow-up period, survival was better in group A (Table 3). Overall, 6 patients in group B had died at the time of follow-up, with 4 deaths occurring in the first year after removal from the waiting list. None of the patients in

Figure 1. Freedom from death during follow-up. Freedom from death was significantly higher in group A than in group B (log-rank method). Follow-up began at time of initial listing on transplant registry ($P < .05$).

group A had died at a median follow-up of 3.7 years (Figure 1). Status IB and need for inotropic therapy as an isolated, dichotomous variable also predicted a worse survival (Figure 2). Survivals at 1 and 3 years were 66.7% and 33.3% for status IB and 100% and 92% for status II ($P < .01$). Patients with dilated cardiomyopathy also had improved survival relative to those with ischemic cardiomyopathy (Figure 3).

Discussion

In this limited retrospective study we sought to determine the survival of patients who were listed for heart transplantation and subsequently removed. Given the natural history of end-stage heart failure, the survival of these patients was expected to be dismal. Interestingly, of the subgroup of patients who had improvement with medical therapy, all were alive at a median follow-up of 3.7 years. Our data suggest that patients in status II, particularly those with dilated cardiomyopathy, have a favorable survival if clinical improvement is observed. These results are remarkable when contrasted with the high mortality expected according to the Framingham study.¹

Improved survival is probably related to advances in the multimodal pharmacotherapy of heart failure. Although the number of patients in this study was small to evaluate the impact of implantable devices, it is also likely that the widespread use of AICDs and resynchronization therapy has further improved survival.^{11,12} This study also highlights the current imperfect science of predicting an indi-

Figure 2. Freedom from death by listing status. Freedom from death was significantly higher in status II than status I patients (log-rank method). Follow-up began at time of initial listing on transplant registry ($P < .05$).

TABLE 3. Outcome and follow-up

Event	Group A (n = 18)	Group B (n = 9)
Death on waiting list (No.)	0	6
Congestive heart failure	0	4
Nonembolic colonic ischemia	0	1
Pulmonary arterial rupture during right heart catheterization	0	1
Total follow-up* (y, median and range)	6.2 (2.0-8.9)	2.9 (0.7-4.8)
Time spent on the waiting list (y, median and range)	3.7 (0.1-7.8)	2.3 (0.6-3.7)

*Follow-up began at time of registration.

vidual patient's response to medical therapy. The patients listed for heart transplantation were all judged to have end-stage heart failure, and all medical treatments had been optimized before their listing. Nevertheless, a subgroup showed clinical improvement during the wait for an allograft. This improvement was to such a degree that removal of these patients from the transplant list was warranted, with continued excellent survival. These data confirm the need for constant reevaluation of UNOS-listed patients.^{7,8}

The modern era of medical and surgical treatment of heart failure has offered many new therapies that have

Figure 3. Freedom from death by etiology of cardiomyopathy. Freedom from death was significantly higher in patients with dilated cardiomyopathy than in those with ischemic cardiomyopathy (log-rank method). Follow-up began at time of initial listing on transplant registry ($P < .05$).

demonstrated improved survival and freedom from heart failure admissions.^{4,5} In fact with optimal medical treatment and device therapy, such as biventricular pacing and AICDs, there has been a considerable change in mortality among patients in end-stage heart failure awaiting cardiac transplantation,^{11,12} even those receiving inotropic support at home.¹³ Surgical options have also expanded, including high-risk coronary revascularization, mitral valve repair, ventricular remodeling, and use of marginal cardiac donors.¹⁴⁻¹⁸ Unfortunately, despite these efforts, the organ donor shortage is a real problem, because the number of cardiac transplantations seems to have reached a plateau. Solutions to address this problem need to be devised to approach the equilibrium point between organ supply and demand.

In successive analyses of the UNOS database through the years, there has been a consistent improvement in survival of transplant recipients as a result of improvements in postoperative care and immunosuppression. Unfortunately, the shortage of donor hearts continues to be a major limiting factor in offering this lifesaving operation to all those waiting on the transplant list. The 2002 UNOS Annual Report listed the number of patients awaiting hearts to be approximately 3700, with an additional 3154 patients added and only 2141 undergoing transplantation.¹⁹

To address methods for improving organ supply, in a recent survey of the transplant medical community consist-

ing of members of the International Society of Heart and Lung Transplantation and the Foundation for Advancement of Cardiac Therapies, 75% of the respondents supported presumed consent, and 70% supported indirect compensation (eg, payment of funeral expenses and charity donations).²⁰ In addition, a large number thought that consultation with next of kin should not be obtained if a donor card had been signed. These provocative issues will likely be the subject of much debate as these matters are further expanded and legislative consideration is given to them.

Kao and colleagues,⁸ in an evaluation of patients who were on the heart transplant list for 6 months or more, reported no survival benefit relative to patients undergoing transplantation within 6 months. The recognized limitation of that study was that most of these patients had continued clinical deterioration and required inotropic support, a condition known to be associated with high mortality.²¹ Our study clearly differs in that most patients were removed from the transplant list because of clinical improvement.

Among other controversies regarding strategies aimed at optimizing outcome, Deng and colleagues²² have suggested the need for revising the current system of organ allocation. In particular, recent improvements in medical and surgical therapies question the survival benefit conferred by heart transplantation on patients in stable condition. Is it perhaps time to conduct a well-designed, prospective randomized trial to assess this notion?

This review is limited by its retrospective nature. As such, certain variables could not be assessed. Although AICDs and biventricular pacemakers have improved outcomes for patients, we could not address this in our study. Functional status and quality of life were not assessed in our cases, although other studies have shown that similar patients who are in stable condition on medical therapy show exercise capacity and self-assessed quality of life similar to those of patients who have undergone transplantation.^{23,24}

In conclusion, this study suggests that a continued re-evaluation of patients on the heart transplant list as UNOS status II is warranted. For patients demonstrating clinical improvement, removal from the transplant list and continued medical management seems prudent in terms of overall survival. If a patient's condition deteriorates at any time, relisting remains an option. For patients who are inotrope dependent, cardiac transplantation remains the criterion standard treatment. Ultimately, the benefit of cardiac transplantation in stable status II patients may need to be determined by a well-planned and orchestrated prospective trial.²⁰

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