

Exercise Capacity for Survivors of Cardiac Transplantation or Sustained Medical Therapy for Stable Heart Failure

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Cardiac transplantation is predicted to improve survival for patients with severe symptoms of heart failure and ejection fraction of 20% or less, but the exercise capacity after cardiac transplantation is less than normal. Patients responding to vasodilators and diuretics have progressive improvement in exercise capacity despite low ejection fraction. We hypothesized that among patients currently considered appropriate for transplantation who could nonetheless subsequently be stabilized on medical therapy tailored to hemodynamic goals, survivors after 6 months of sustained medical therapy would demonstrate exercise capacity comparable to that of survivors of transplantation. Of 146 patients referred, 118 (81%) were discharged on tailored therapy without transplantation, and 88 (60%) were stable for at least 1 month. Stability after discharge was more likely in patients with lower right atrial pressures and better renal function on therapy. Of the 88 stable patients, 45 patients were listed for transplant, and 43 were ineligible or unwilling. From these patients, 42 survivors for more than 6 months follow-up after cardiac transplantation or tailoring of medical therapy underwent exercise testing. Baseline functional and hemodynamic status and left ventricular ejection fraction ($15 \pm 4\%$) were not different between the transplant and sustained medical survivor groups at the time of initial evaluation. After 14 ± 6 months, left ventricular ejection fraction had increased to $62 \pm 7\%$ after transplantation ($p < 0.01$) and only $22 \pm 9\%$ after sustained medical therapy ($p < 0.05$). However, there were no significant differences in the maximum workload, oxygen uptake, anaerobic threshold, or maximum oxygen pulse between survivors of cardiac transplantation and survivors on sustained medical therapy. For patients with severe heart failure who can be stabilized on tailored medical therapy without transplantation (60% of patients referred), cardiac transplantation improves ejection fraction without comparable improvement in exercise capacity beyond that achieved after sustained tailored therapy. (*Circulation* 1990;81:78–85)

In contrast to the early years of cardiac transplantation, many eligible patients can now be stabilized on maximal medical therapy tailored to hemodynamic goals for advanced heart failure, despite low ejection fraction, history of New York Heart Association functional class IV symptoms, and pre-

vious decompensation.¹ While this therapy is instituted to improve status during the waiting period before transplantation, such patients and their referring physicians frequently ask whether transplantation remains indicated. The current 1-year survival after cardiac transplantation is 80–90%² compared with less than 50%, which has been reported for patients with ejection fraction of less than 20% and severe symptoms of heart failure.^{3–5} However, many patients are unwilling to accept the rigors of the post-transplantation regimen unless they will be accompanied by improvements in functional status as well as in ventricular function and survival. Exercise capacity is a major component of functional status and has been shown to be good after cardiac transplantation, although not equivalent to that of the normal population.^{6–10} Effective medical therapy can also allow progressive improvement in exercise capac-

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ity over 2–6 months in responding patients^{11–13} for whom the relative functional benefit of cardiac transplantation has not been established. We hypothesized that among patients considered appropriate for transplantation by current criteria¹⁴ who can be stabilized on medical therapy, survivors after 6 months of sustained medical therapy would demonstrate exercise capacity comparable to that of survivors after cardiac transplantation.

For this study, we identified the patients initially referred with severe heart failure who were clinically stable at 1 month after transplant evaluation and discharge on therapy tailored to hemodynamic goals for advanced heart failure. Within that population, we compared ventricular function and exercise capacity for those patients who survived at least 6 months on sustained medical therapy and those patients with comparable baseline status who survived at least 6 months after cardiac transplantation.

Methods

All patients over 18 years admitted for cardiac transplantation evaluation at University of California, Los Angeles Medical Center from September 1985 through September 1987 were identified. Patients with diagnoses other than chronic dilated left ventricular failure were not analyzed in this study, which also excluded patients with less than a 6-month history of nonischemic cardiomyopathy, due to their high frequency of spontaneous improvement in ventricular function.¹⁵

Initial Evaluation and Therapy

At the time of admission, patients were routinely interviewed by one of three cardiologists to determine the hospitalization history and the length and nature of symptoms associated with congestive heart failure. At that time, the interviewer graded symptom severity on scales of 0 to 4; activity limitation grade 4 being bedridden; grade 3, walking at home but less than one block; grade 2, unlimited flat walking; grade 1, unlimited routine activity; orthopnea grade 4 being sitting to breathe; grade 3, sleeping with three pillows or frequent paroxysmal nocturnal dyspnea; grade 2, sleeping with two pillows or occasional paroxysmal dyspnea; grade 1, sleeping with rare difficulty; grade 4 of right-sided symptoms being constant discomfort from splanchnic congestion or peripheral edema; grade 3, frequent daily discomfort; grade 2, discomfort several times weekly; grade 1, rare discomfort. At the initial time of study, exercise testing was not routine in patients with severely symptomatic heart failure and was performed only to confirm cardiovascular capacity in patients considered too well for transplantation. Initial peak oxygen uptake, workload, and exercise times are not available for the patients in this study, all of whom had dyspnea at rest or with minimal activity.

Coronary angiography was performed before or during evaluation in all patients. Right-heart catheterization was performed after admission, with base-

line hemodynamics measured in the postabsorptive state 2–4 hours after catheter insertion to determine pulmonary vascular resistance and to guide therapy.

Medical therapy with intravenous and subsequent oral vasodilators and diuretics was tailored to approach hemodynamic goals of pulmonary capillary wedge pressure of 15 mm Hg or less, right atrial pressure of 8 mm Hg or less, and systemic vascular resistance of $1,200 \text{ dynes} \cdot \text{sec} \cdot \text{cm}^{-5}$ or less, while maintaining systolic blood pressure of 80 mm Hg or more, as previously described to result in maximal cardiac output¹⁶ and sustained clinical response in this population.¹ Before removal of the catheter, hemodynamics after at least 24 hours of oral therapy were recorded.

Patients were excluded from further analysis if transplantation or death occurred before discharge or if major medical contraindications or history of refractory noncompliance were identified according to current standard criteria.¹⁷ All patients were discharged on oral vasodilators (either captopril or hydralazine and isordil) tailored as above, digoxin if not contraindicated, and oral furosemide or bumetanide to be adjusted to maintain weight within 2 lb of discharge weight, with intermittent metolazone to be added if necessary.

Outpatient Stability and Therapy

At the time of discharge, transplantation was recommended to all patients who were eligible. Four patients who underwent transplantation and one who died within the first 2 weeks were excluded, as stability on medical therapy could not be determined. All other patients were followed weekly and evaluated for clinical stability within the first month after discharge. Patients were defined as unstable if by 1 month weight on oral diuretics could not be maintained within 2 lb of discharge weight, systolic blood pressure of 80 mm Hg or more could not be maintained, blood urea nitrogen was more than 60 mg/dl or increasing, sodium was less than 130 meq/l or decreasing, angina in patients with coronary artery disease occurred more than three times weekly, or symptomatic ventricular arrhythmias occurred.

At 1 month, 88 patients were considered stable (Table 1). Cardiac transplantation had been recommended to all 66 eligible patients. The other 22 patients were being followed with conditions believed to contraindicate transplantation at that time but to merit future reconsideration (see "Results"). Tailored medical therapy was continued for all 88 patients throughout the follow-up period or until cardiac transplantation was performed. No outpatient transplant candidate required rehospitalization to await transplantation.

Cardiac transplantation was performed using standard protocols of donor-recipient matching, donor organ evaluation, and surgical technique. Triple immunosuppression regimen was used in the majority of patients.¹⁷ Moderate rejection was diagnosed and treated according to standard practice.¹⁸ Those

TABLE 1. Selection of Groups for Comparison

| | <i>n</i> |
|--|----------|
| Patients without major transplant contraindications | 146 |
| Transplanted during initial hospitalization | 23 |
| Died in hospital without transplant | 5 |
| Died 1 week after discharge | 1 |
| Transplanted within 2 weeks of discharge | 4 |
| Patients unstable in the first month after discharge | 25 |
| Potential candidates stable at 1 month | 88 (60%) |
| Awaiting transplant | 45 |
| Declined transplant | 1 |
| Died waiting | 9 |
| Died after transplant | 5 |
| Relocated | 1 |
| Short follow-up | 5 |
| Restriction to exercise | 2 |
| Patients (group 1) | 22 |
| Planning sustained medical therapy | 43 |
| Chose transplant after 6 months | 3 |
| Died | 10 |
| Relocated | 2 |
| Short follow-up | 7 |
| Restriction to exercise | 1 |
| Patients (group 2) | 20 |

patients who underwent transplantation did not undergo the follow-up assessment of exercise capacity until at least 2 months after the most recent therapy for rejection.

At 1 month after transplantation or revision of medical therapy, all patients were instructed to begin a progressive walking program consisting of 5 days a week walking one half block, increasing distance weekly to achieve 1–2 miles performed outside or in enclosed malls in inclement weather. Patients were reinstructed at every clinic visit, but compliance with exercise instructions was not specifically assessed.

Assessment of Survivors

The remaining 22 patients surviving more than 6 months after transplantation (15 ± 6 months; group 1) were compared with those 20 patients surviving after more than 6 months (12 ± 5 months) of sustained medical therapy (group 2), who were not initially placed on the transplant list for minor contraindications or unwillingness, as detailed below.

Echocardiography was routinely performed in group 1 patients at the time of each endomyocardial biopsy and in group 2 patients at 6–12-month intervals during sustained medical therapy. Ejection fraction was calculated from computer-assisted digitization of left ventricular volumes, calculated according to Simpson's rule from standard apical views.¹⁹

Patients underwent informed consent before the performance of exercise testing. Patients were tested initially with a 6-minute walk during which distance was measured after 6 minutes of the patient's self-

determined pace along an inside corridor, as described previously by Lipkin et al.²⁰ Later on the same day, patients exercised on a cycle ergometer at a constant workload of 20 W for 6 minutes. After a 2–3-minute rest period, patients then performed symptom-limited bicycle exercise during which the work rate was continuously increased at a rate of 15 W/min. During the cycle ergometer exercise, oxygen uptake and carbon dioxide output were measured breath-by-breath by a Medical Graphics System 2001 analyzer. Peak oxygen uptake was measured and compared with the predicted maximal based on height, weight, gender, and age as described by Wasserman et al, which reflects lean body mass in the presence of excess body weight.²¹ As these patients generally did not demonstrate a plateau of oxygen uptake consistent with a true maximal value, the symptom-limited peak oxygen consumption is described, with corresponding ventilatory measurements. Anaerobic threshold was assessed using the V-slope method in addition to ventilatory criteria. The ratio of oxygen uptake increase to work rate increase measured the values obtained after steady-state 20-W exercise and peak exercise. Peak oxygen pulse was determined by dividing peak oxygen uptake by peak heart rate.

All values are given as mean \pm SD. Comparisons between groups were made with unpaired Student's *t* tests and within groups with paired *t* tests, with $p < 0.05$ considered significant. To maximize sensitivity for group differences, no adjustment was made for multiple comparisons.

Results

Early Stability After Discharge

Hospital discharge without transplantation was possible for 118 patients without major contraindications to transplantation (Table 1). Transplantation (four patients) or sudden death (one patient) occurred in five patients during the next 2 weeks. By 1 month, 25 patients were considered unstable due to continued weight gain despite increasing oral diuretics (16 patients, five of whom also had deteriorating renal function), angina (four patients), severe hypotension (three patients), declining serum sodium (one patient), or syncope (one patient). These 25 patients who became unstable after discharge did not differ from the stable survivor groups in general characteristics except for a slightly higher ejection fraction (Table 2). At the time of initial evaluation, the hemodynamic status of the patients who became unstable after discharge was no worse than that of the patients who remained stable during the first month of follow-up. However, the response to tailored therapy during hospitalization was less favorable, with higher final filling pressures, lower cardiac index and mean arterial pressure, and worsening renal function in the unstable group. After identification of instability, 17 of these patients underwent transplantation, seven died, and one is living on dialysis.

TABLE 2. Unstable Patients and Stable Survivor Groups: Baseline Characteristics

| | Patients unstable 1 mo after discharge | Patients stable at 1 mo | |
|---|--|---|--|
| | | Group 1: subsequent transplant survivors (n=22) | Group 2: subsequent medical survivors (n=20) |
| Age (yr) | 47±10 | 48±8 | 48±10 |
| Male | 22/25 | 20/22 | 19/20 |
| Ejection fraction | 0.18±0.07* | 0.15±0.04 | 0.15±0.04 |
| Coronary artery disease (%) | 13/25 (52) | 12/22 (55) | 6/20 (30) |
| New York Heart Association functional class | 3.7±0.4 | 3.4±0.4 | 3.7±0.4 |
| Prior vasodilator therapy (%) | 17/25 (68) | 16/22 (73) | 15/20 (75) |
| Transferred as inpatient (%) | 8/25 (32) | 8/22 (36) | 11/20 (55) |
| Activity limitation† | 3.3±0.8 | 3.5±0.5 | 3.4±0.6 |
| Orthopnea† | 2.7±1.4 | 2.8±1.2 | 2.6±1.3 |
| Right-sided symptoms† | 1.6±0.9 | 1.4±1.1 | 1.8±1.3 |

* $p < 0.05$ between unstable and stable patients (†graded on 0–4 scale as described in “Methods”).

Of the 88 patients demonstrating early stability, 19 died without transplantation, nine of whom had been on the transplant list and 10 of whom had been on sustained medical therapy. All of these deaths except one occurred suddenly. Five patients died after transplantation. These patients and 15 who had relocated or had less than 6 months follow-up before evaluation were excluded from comparison, as were one patient who later declined transplantation and three who chose transplantation after 6 months (Table 1). Vigorous exercise was judged to be contraindicated in two transplant survivors due to aseptic necrosis of the hip and thoracic aneurysm dissection and one medical survivor with a massive left ventricular thrombus.

Profile of Survivor Groups

The initially stable patients who subsequently survived cardiac transplantation were compared with those who survived sustained medical therapy. At the time of initial evaluation, the patients who survived transplantation for more than 6 months (group 1) were not different from the patients surviving more than 6 months on sustained medical therapy (group 2) in terms of initial left ventricular ejection fraction, previous oral vasodilator therapy, or frequency of hospital transfer for urgent evaluation (Table 2). During the 6 months before evaluation, there were an average of 2.1 hospitalizations for heart failure in group 1 patients and 2.7 in group 2 patients. The severity of activity limitation, orthopnea, and symp-

TABLE 3. Unstable Patients and Stable Survivor Groups

| | Patients unstable at 1 mo | | Patients stable at 1 mo | | | |
|--|---------------------------|---------------------|-------------------------|---------------------|----------------|---------------------|
| | (n=25) | | Group 1 (n=22) | | Group 2 (n=20) | |
| | Initial | On tailored therapy | Initial | On tailored therapy | Initial | On tailored therapy |
| Cardiac index (l/min/m ²) | 1.8±0.4 | 2.5±0.5* | 2.0±7 | 2.7±0.5 | 2.0±0.4 | 2.9±0.7 |
| Pulmonary capillary wedge pressure (mm Hg) | 32±6 | 18±7* | 30±10 | 15±6 | 27±9 | 14±5 |
| Right atrial pressure (mm Hg) | 14±6 | 8±4* | 12±6 | 5±3 | 14±8 | 5±2 |
| Mean arterial pressure (mm Hg) | 81±22 | 68±23* | 86±10 | 79±11 | 85±10 | 74±8 |
| Systemic vascular resistance (dynes · sec · cm ⁻⁵) | 1,780±700 | 1,030±420 | 1,706±700 | 1,200±200† | 1,610±440 | 1,050±150† |
| Heart rate (beats/min) | 94±17 | 94±15 | 95±15 | 93±10 | 96±14 | 94±16 |
| Serum creatinine (mg/dl) | 1.2±0.3 | 1.5±0.6* | 1.1±0.2 | 1.2±0.2 | 1.3±0.3 | 1.2±0.3 |
| Blood urea nitrogen (mg/dl) | 30±20 | 37±24* | 23±13 | 24±12 | 27±13 | 23±12 |
| Serum sodium (meq/l) | 135±5 | 133±6 | 136±6 | 134±5 | 134±6 | 134±4 |

* $p < 0.05$ between unstable patients and stable patients at 1 month.

† $p < 0.05$ between transplant survivors and medical survivors.

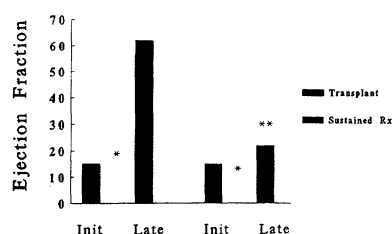


FIGURE 1. Bar graphs of left ventricular ejection fractions at the time of initial evaluation (Init) and late after cardiac transplantation (22 patients, 15 ± 6 months) or sustained medical therapy (20 patients, 12 ± 5 months). * $p < 0.05$, difference between initial and late ejection fraction within groups; ** $p < 0.05$ difference between final ejection fractions between groups.

toms of ascites or peripheral edema were similar at baseline in both groups. Angina was not the major limitation in any patient but occurred more than twice weekly in three group 1 patients and one group 2 patient.

The hemodynamic profiles at the time of referral and during revision of medical therapy before discharge were not different between the two groups, with average initial cardiac index 2.0 l/min/m^2 in both groups, except for lower final systemic vascular resistance in group 2 (Table 3). Oral drug regimens at the time of initial discharge included captopril in 11 group 1 patients and 10 group 2 patients, hydralazine in 11 group 1 patients and 12 group 2 patients, and nitrate preparations in 19 group 1 patients and 14 group 2 patients. Cardiac transplantation was recommended to all patients in group 1 and to seven patients in group 2, who were at that time undecided. The remaining 13 patients in group 2 had unresolved

contraindications: psychologic (four), financial (three), diabetes (two), pulmonary (two), age (one), or neurologic limitations (one).

Ejection Fraction and Exercise Capacity

Assessment of left ventricular function 15 ± 6 months after cardiac transplantation showed left ventricular ejection fraction to have increased to within normal limits (Figure 1). Ejection fraction also increased after 12 ± 5 months in patients on sustained medical therapy but remained severely reduced compared with that after cardiac transplantation.

Exercise capacity was assessed at the same time as left ventricular function and was similar in the two groups (Table 4). The average distances covered in 6 minutes of voluntary walking were the same. All patients were able to complete 6 minutes of steady-state 20-W submaximal bicycle exercise without evidence of anaerobic metabolism. Peak oxygen uptake in both absolute measurement and percent of predicted maximal values was not higher in the patients who had undergone cardiac transplantation. The anaerobic thresholds, which could be identified by the V-slope method and concordant ventilatory criteria in all but two patients, did not differ between the two groups. In group 1, the peak R (respiratory exchange ratio) was slightly higher and the ventilatory equivalent for CO_2 was significantly higher, suggesting effort at least as strenuous as that for group 2 patients. The increments of oxygen uptake in relation to work rate and the peak oxygen pulses were also the same for the two groups. Limitation could be attributed to decreased aerobic capacity rather than musculoskeletal or volitional factors in all patients except one group 1 patient with claudication. Symptoms leading to exercise termination in group 1 were dyspnea in six patients and fatigue in 16; for group 2, dyspnea in eight and fatigue in 12.

Discussion

This study demonstrates that among patients with severe symptoms of heart failure and ejection fraction of 20% or less who can be stabilized (60% of patients referred to this program), those who survive more than 6 months on sustained medical therapy achieve exercise capacity that is comparable to that of patients surviving after cardiac transplantation. This was shown although this population originally presented with deteriorating status, evidenced by clinical and hemodynamic profiles, an average of more than two hospitalizations for heart failure during the 6 months preceding evaluation, and apparent failure of previous standard therapy, which usually included oral vasodilators. The unexpected similarity of ultimate exercise performance between the two survivor groups despite the large difference in ejection fraction reflects both the greater potency of sustained effective afterload reduction and the greater limitations of the transplanted heart than are generally recognized.

TABLE 4. Exercise Capacity of Survivors

| | Group 1 (after transplant) | Group 2 (sustained medicine) |
|--|----------------------------------|------------------------------------|
| 6-Min walk (ft) | $1,460 \pm 180$ | $1,430 \pm 190$ |
| Peak watts | 103 ± 20 | 103 ± 28 |
| Peak O_2 uptake (ml) | $1,360 \pm 340$ | $1,440 \pm 350$ |
| Peak O_2 uptake (ml/kg) | 17 ± 4 | 19 ± 4 |
| % Predicted max | 60 ± 14 | 62 ± 9 |
| $\dot{\text{V}}\text{O}_2/\text{work rate}$ (ml/W) | 7.8 ± 3 | 7.9 ± 3 |
| AT (ml O_2) | 820 ± 270 | 960 ± 330 |
| $\text{R}(\dot{\text{V}}\text{CO}_2/\dot{\text{V}}\text{O}_2)$ at peak exercise | 1.17 ± 0.12 | 1.13 ± 0.08 |
| $\text{VE}/\dot{\text{V}}\text{CO}_2$ at peak exercise | 43 ± 6 ($p < 0.05$) | 37 ± 9 |
| Peak heart rate (beats/min) | 137 ± 18 | 145 ± 20 |
| Peak O_2 pulse (ml/beat) | 10 ± 2 | 10 ± 2 |

AT, anaerobic threshold determined by V-slope and ventilatory criteria; R, respiratory exchange ratio; $\dot{\text{V}}\text{CO}_2$, carbon dioxide release; VE, minute ventilation; $\dot{\text{V}}\text{O}_2$, oxygen uptake.

During the era that has seen major advances in cardiac transplantation, afterload reduction has also evolved.^{22–24} For patients with severe heart failure referred for transplantation, afterload and preload reduction with high-dose vasodilators and diuretics has been tailored specifically to hemodynamic goals, which not only allows the filling pressure to be substantially below the level causing symptomatic congestion¹⁶ but also minimizes the mitral regurgitation present during rest and exercise in these patients.^{25,26} Such therapy frequently improves clinical status acutely after referral, even when previous vasodilator administration has been ineffective.¹ It has previously been shown that for patients transferred urgently from other hospitals, the efficacy of tailored therapy in allowing hospital discharges without transplantation could not easily be predicted by the initial hemodynamic and renal profile, although these were frequently worse in patients who could not be discharged without transplantation.¹ Similarly, among patients who can be discharged, initial hemodynamics *before* therapy did not predict stability at 1 month, which was more common in patients with lower final right atrial pressure, creatinine, and blood urea nitrogen *after* therapy. Because patients who will initially or subsequently fail tailored therapy cannot be predicted by initial clinical history or hemodynamics, all patients with severely symptomatic heart failure deserve a trial of tailored therapy to improve immediate status, regardless of whether future transplantation is planned.

While selected patients with good exercise capacity despite severely reduced ejection fraction have been previously described,^{27,28} this study of patients with initial ejection fraction of 20% or less selected *only* for stability after 1 month of revised medical therapy and subsequent survival over 6 months showed that most such patients can achieve more than 50% of predicted maximal capacity. The threefold to fourfold increase in left ventricular volumes that generally occurs²⁵ allows an adequate stroke volume at rest and exercise despite severely reduced ejection fraction, provided that mitral regurgitation can be minimized.²⁶ Exercise-induced peripheral vasodilation may further improve ejection fraction and tachycardia increase cardiac output.²⁷

The left ventricular ejection fraction was normal after transplantation in our population and in others.^{6,10} Exercise capacity after transplantation was also good but was less than predicted for normal subjects. While it is possible that some patients on chronic immunosuppression may be limited by musculoskeletal problems, evidence of increasing anaerobic metabolism was present in all but one of our transplant patients before peak exercise. Transplant patients have previously been shown to have higher peak lactate levels and ventilatory equivalents⁷ and lower peak work rates and peak oxygen uptakes than normal (101 W and 1.5 l, 70% normal by Kavanaugh, compared with 103 W and 1.4 l, 60% of normal predicted in our group). Heart rate and contractility

do increase during exercise after transplantation, as a result of increased circulating catecholamines,^{6,8} but the maximal cardiac output is lower than normal maximal cardiac output.^{6,9} While the limitation results in part from decreased maximal heart rate, the low maximal oxygen pulse is consistent with the low peak stroke volumes that have been described.^{8–10} While left ventricular ejection fraction is normal, left ventricular size may be low-normal or low in some patients²⁹ and compliance reduced,^{30–31} particularly during exercise.¹⁰ Rejection, hypertension, and cyclosporin all may contribute to myocardial stiffness after cardiac transplantation.

Exercise capacity is only one determinant of quality of life. Other aspects of life satisfaction have been compared in patients with stable heart failure and patients after cardiac transplantation.³² Patient adjustment to illness questionnaires showed similar overall awareness of illness in both groups, with slightly greater dysfunction in social functioning for heart failure patients who viewed themselves as able to perform less activity than did the transplant patients (estimated metabolic equivalent, 5.3 vs. 7.9 METS). The two groups described similar intensity of general anxiety and depression. The similarity in perception between the two groups may reflect in part similar medical regimens (average 16 daily doses for transplant patients and 13 for heart failure patients), while unexpected hospital days were more frequent after cardiac transplantation.³²

Limitations

This study is limited by the lack of a true control group of patients with hemodynamically stable heart failure on tailored medical therapy against which to compare cardiac transplantation. It is currently not acceptable to randomize patients to sustained medical therapy or transplantation, due to the potential impact on survival. The seven patients who were undecided may well have perceived less disability than those who accepted transplantation initially. However, all clinical and hemodynamic parameters of disease severity obtained at baseline suggested the two groups to be comparable. The study is limited by the lack of objective information about initial exercise capacity, which was not at that time formally tested in patients demonstrating obvious limitations during minimal activity. Routine assessment of peak oxygen consumption and anaerobic threshold, which are less variable than exercise time and workload,³³ may prove in the future to better identify patients who will need transplantation. However, it should be emphasized that regardless of any unrecognized baseline differences, *both* groups represent patients with ejection fraction of 20% or less for whom cardiac transplantation would have been considered appropriate according to current clinical and hemodynamic guidelines¹⁴ and might have been performed with the expectation of better functional capacity than that achieved by survivors of sustained medical therapy.

It is unlikely that longer observation on the same regimen would have revealed differences in exercise capacity between groups. Limitation that may result from peripheral metabolic muscle adaptation^{34,35} does not rapidly resolve, and the maximal benefit of optimal medical therapy may be delayed for several months.¹¹⁻¹³ Peripheral vasodilator reserve is decreased in heart failure and did not normalize until 3 months after cardiac transplantation.³⁶ However, all patients in this study were followed for at least 6 months, with average time of 12 months for medical patients and 15 months for transplant patients. Further improvements for both groups would probably have resulted from formal exercise training,³⁷ which has been shown to increase peak oxygen consumption by 23% in heart failure patients³⁸ and 19% in cardiac transplant patients.⁹

Tailored Therapy Before Cardiac Transplantation

Cardiac transplantation is currently limited by the deficit between the estimated 2,000 donor hearts yearly and 20,000 potential recipients.³⁹ Referrals continue to increase, but the number of transplants performed yearly is no longer changing. Survival after transplantation exceeds that of referred patients who do not undergo transplantation, particularly when medical therapy is not systematically tailored for advanced heart failure and early stability is not monitored.⁴⁰ However, patients with ejection fraction of less than 20% and severe symptoms of heart failure cannot all undergo transplantation, although it is predicted to improve their survival.⁴¹ Even for accepted candidates, the waiting time frequently exceeds 6 months. Thus, all patients with severe heart failure referred for transplantation should undergo afterload reduction tailored for this population, regardless of the apparent inadequacy of previous therapy. This will allow identification of the subgroup of truly unstable patients, who may derive the greater overall benefit from transplantation and, thus, deserve the higher priority. Decisions regarding those patients who appear stable at 1 month on tailored therapy should reflect individual relative values placed on the potential increment of increased survival expected from transplantation as compared with the lack of major improvement in exercise capacity or quality of life³² and greater dependence on tertiary medical care. Our results also suggest that patients surviving more than 6 months on medical therapy while awaiting transplantation may deserve reevaluation regarding their need for surgery. With further evolution of cardiac transplantation and medical therapy for heart failure, the relative benefits of each should undergo continual reassessment in relation to all of the populations referred for evaluation.

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References

1. Stevenson LW, Dracup KA, Tilliach JH: Efficacy of medical therapy tailored for severe congestive heart failure in patients transferred for urgent cardiac transplantation. *Am J Cardiol* 1988;58:1046-1050
2. Fragomeni LS, Kaye MPL: The Registry of the International Society for Heart Transplantation: Fifth official report. *J Heart Transplant* 1988;7:249-253
3. Likoff MJ, Chandler SL, Kay HR: Clinical determinants of mortality in chronic congestive heart failure secondary to idiopathic dilated or ischemic cardiomyopathy. *Am J Cardiol* 1987;59:634-638
4. Wilson JR, Schwartz JS, St. John Sutton M, Ferraro N, Horowitz LN, Reichel N, Josephson ME: Prognosis in severe heart failure: Relation to hemodynamic measurements and ventricular ectopic activity. *J Am Coll Cardiol* 1983;2:403-409
5. Cohn JN: Clinical definitions and studies, in Braunwald E, Mick MB, Watson J (eds): *Congestive Heart Failure*. New York, Grune & Stratton, 1982, p 13
6. McLaughlin PR, Kleinman JH, Martin RP, Doherty PW, Reitz B, Stinson EB, Daughters GT, Ingels NB, Alderman EL: The effect of exercise and atrial pacing on left ventricular volume and contractility in patients with innervated and denervated hearts. *Circulation* 1987;58:476-483
7. Savin WM, Haskell WL, Schroeder JS, Stinson EB: Cardiorespiratory responses of cardiac transplant patients to graded, symptom-limited exercise. *Circulation* 1980;62:55-60
8. Pope SE, Stinson EB, Daughters GT, Schroeder JS, Ingels NB, Alderman EL: Exercise response of the denervated heart in long term cardiac transplant recipients. *Am J Cardiol* 1980;46:213-218
9. Kavanaugh T, Yacoub MH, Mertens DJ, Kennedy J, Campbell RB, Sawyer P: Cardiorespiratory responses to exercise training after orthotopic cardiac transplantation. *Circulation* 1988; 77:162-168
10. Hosenpud JD, Morton MJ, Pantley GA, Wilson RA, Norman DJ, Cobanoglu MA, Starr A: Increased exercise filling pressure and reduced exercise tolerance despite normal ejection fractions one year following transplantation (abstract). *J Heart Transplant* 1988;53:7
11. Rubin SA, Chatterjee K, Parmley WW: Metabolic assessment of exercise in chronic heart failure patients treated with short-term vasodilators. *Circulation* 1980;61:543-548
12. Kramer BL, Massie BM, Topic N: Controlled trial of captopril in chronic heart failure: A rest and exercise hemodynamic study. *Circulation* 1983;67:807-815
13. Franciosa JA, Dunkman WB, Leddy CL: Hemodynamic effects of vasodilators and long-term response in heart failure. *J Am Coll Cardiol* 1984;3:1521-1530
14. Copeland JG, Emery RW, Levinson MM, Icenogle TB, Carrier M, Ott RA, Copeland JA, McAleer-Rhenman MJ, Nicholson SM: Selection of patients for cardiac transplantation. *Circulation* 1987;75:1-9
15. Dec GW, Placios IK, Fallon JT, Aretz HT, Mills J, C-S Lee D, Johnson RA: Active myocarditis in the spectrum of acute dilated cardiomyopathies. *N Engl J Med* 1985;312:885-890
16. Stevenson LW, Tillisch JH: Maintenance of cardiac output with normal filling pressures. *Circulation* 1986;74:1303-1308
17. Stevenson LW, Laks H, Terasaki PI, Kahan BD, Drinkwater D: Cardiac transplantation: Selection, immunosuppression and survival. *West J Med* 1988;572-582
18. Billingham ME: Diagnosis of cardiac rejection by endomyocardial biopsy. *Heart Transplant* 1981;1:25-30
19. Weyman AE, Doty WD: Left ventricle, in Weyman AE (ed): *Cross-Sectional Echocardiography*. Philadelphia, Lea & Febiger, 1982, p 267
20. Lipkin DP, Scriven AJ, Crake T, Poole-Wilson PA: Six minute walking test for assessing exercise capacity in chronic heart failure. *Br Med J* 1986;292:653-656
21. Wasserman K, Hansen JE, Sue DU, Whipp BJ: *Principles of Exercise Testing and Interpretation*. Philadelphia, Lea & Febiger, 1987, p 76

22. Cohn JN: Vasodilator therapy for heart failure: the influence of impedance on left ventricular performance. *Circulation* 1973;48:5-8
23. Chatterjee K, Parmley WW: Vasodilator therapy for acute myocardial infarction and chronic congestive heart failure. *J Am Coll Cardiol* 1983;1:133-153
24. Cohn JN, Archibald DG, Ziesche S, Franciosa JA, Harston WE, Tristani FE, et al: Effect of vasodilator therapy on mortality in chronic congestive heart failure. *N Engl J Med* 1986;314:1547-1552
25. Stevenson LW, Belil D, McKay MG, Brunken RC, Schwaiger M, Tillisch J, Schelbert HR: Effects of afterload reduction on left ventricular volume and mitral regurgitation in severe congestive heart failure. *Am J Cardiol* 1987;60:654-658
26. Stevenson LW, Brunken RC, McKay MG, Belil D, Schelbert HR, Tillisch J: Afterload reduction with vasodilators and diuretics reduces mitral regurgitation during upright exercise in advanced heart failure. *J Am Coll Cardiol* (in press)
27. Higginbotham MB, Morris KG, Conn EH, Coleman RE, Cobb FR: Determinants of variable exercise performance among patients with severe left ventricular dysfunction. *Am J Cardiol* 1983;51:52-60
28. Litchfield RL, Kerber RE, Bengt JW, Mark AL, Sopko J, Bhatnagar RK, Marcus ML: Normal exercise capacity in patients with severe left ventricular dysfunction: Compensatory mechanisms. *Circulation* 1982;66:129-134
29. Stevenson LW, Dadourian BJ, Child JS, Clark SH, Laks H: Mitral regurgitation after cardiac transplantation. *Am J Cardiol* 1987;60:119-123
30. Valentine H, Appleton C, Hatle L, Hunt S, Oyer P, Baldwin J, Stinson E, Shumway NE: Doppler echocardiographic evaluation of restrictive cardiomyopathy in heart transplant recipients (abstract). *J Heart Transplant* 1986;5:374
31. Young JB, Leon CA, Short D, Noon GP, Lawrence C, Whisenand HH, Pratt CM, Goodman DA, Weilbaecher D, Quinones MA, DeBakey ME: Evolution of hemodynamics after orthotopic heart and heart-lung transplantation: Early restrictive patterns persisting in occult fashion. *J Heart Transplant* 1987;6:34-43
32. Walden JA, Stevenson LW, Dracup KA, Wilmarth J, Kobashigawa J, Moriguchi J: Cardiac transplantation may not improve quality of life for patients with stable heart failure. *Circulation* 1988;78(suppl II):II-217
33. Kappler J, Ziesche S, Nelson J, Francis GS: Reproducibility of hemodynamic and gas exchange data during exercise in patients with stable congestive heart failure. *Heart Failure* 1986;4:157-163
34. Weiner DH, Fink LI, Maris J, Jones RA, Chance B, Wilson JR: Abnormal skeletal muscle bioenergetics during exercise in patients with heart failure: Role of reduced muscle blood flow. *Circulation* 1986;73:1127-1136
35. Massie B, Conway M, Yange R, Frostick S, Ledinghorn J, Sleight P, Radda G, Rajagopalan B: Skeletal muscle metabolism in patients with congestive heart failure: Relation to clinical severity and blood flow. *Circulation* 1987;77:1009-1019
36. Sinoway LI, Minotti JR, Davis D, Pennock JL, Burg JE, Musch TI, Zelis R: Delayed reversal of impaired vasodilation in congestive heart failure after heart transplantation. *Am J Cardiol* 1988;61:1076-1079
37. Conn EH, Williams RS, Wallace AG: Exercise responses before and after physical conditioning in patients with severely depressed left ventricular function. *Am J Cardiol* 1982;49:296-300
38. Sullivan MJ, Higginbotham MB, Cobb FR: Exercise training in patients with severe left ventricular dysfunction. *Circulation* 1988;78:506-515
39. Evans RW, Manninen DL, Garrison LP, Maier AM: Donor availability as the primary determinant of the future of heart transplantation. *JAMA* 1986;255:1982-1988
40. Stevenson LW, Fowler MB, Schroeder JS, Stevenson WG, Dracup KA, Find V: Poor survival of patients with idiopathic cardiomyopathy considered too well for transplantation. *Am J Med* 1987;83:871-876
41. Keogh AM, Freund J, Baron DW, Hickie JB: Timing of cardiac transplantation in idiopathic dilated cardiomyopathy. *Am J Cardiol* 1988;61:418-422

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