Value of Peak Exercise Oxygen Consumption for Optimal Timing of Cardiac Transplantation in Ambulatory Patients With Heart Failure

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Background. Optimal timing of cardiac transplantation in ambulatory patients with severe left ventricular dysfunction is often difficult. To determine whether measurement of peak oxygen consumption (Vo$_2$) during maximal exercise testing can be used to identify patients in whom transplantation can be safely deferred, we prospectively performed exercise testing on all ambulatory patients referred for transplant between October 1986 and December 1989.

Methods and Results. Patients were assigned into one of three groups on the basis of exercise data: Group 1 (n=35) comprised patients accepted for transplant (Vo$_2$$\leq$14 ml/kg/min); group 2 (n=52) comprised patients considered too well for transplant (Vo$_2$$>$14 ml/kg/min); and group 3 (n=27) comprised patients with low Vo$_2$ rejected for transplant due to noncardiac problems. All three groups were comparable in New York Heart Association functional class, ejection fraction, and cardiac index (p=NS). Pulmonary capillary wedge pressure was significantly lower in group 2 than in either group 1 or 3 (p<0.05), although there was wide overlap. Patients with preserved exercise capacity (group 2) had cumulative 1- and 2-year survival rates of 94% and 84%, which are equal to survival levels after transplantation. In contrast, patients rejected for transplant (group 3) had survival rates of only 47% at 1 year and 32% at 2 years, whereas patients awaiting transplantation (group 1) had a survival rate of 70% at 1 year (both p<0.005 versus patients with Vo$_2$$>$14 ml/kg/min). All deaths in group 2 were sudden. By univariate and multivariate analyses, peak Vo$_2$ was the best predictor of survival, with only pulmonary capillary wedge pressure providing additional prognostic information.

Conclusions. These data suggest that cardiac transplantation can be safely deferred in ambulatory patients with severe left ventricular dysfunction and peak exercise Vo$_2$ of more than 14 ml/min/kg. (Circulation 1991;83:778–786)

In 1988, more than 1,500 cardiac transplants were performed in the United States with an average 1-year survival rate of 85%. An increased awareness and acceptance by the medical community has resulted in a sharp increase in referral of patients for cardiac transplantation. Although many patients are desperately ill when referred and require intravenous inotropic or mechanical support, a larger percentage are being referred earlier in the course of their diseases and are ambulatory. Selection criteria for prospective candidates has primarily focused on New York Heart Association (NYHA) functional class, resting ejection fraction, and hemodynamic data. However, NYHA class is subject to both physician and patient bias, and frequently the resting indexes of cardiac function do not correlate with the clinical manifestations of heart failure. With the increasing number of candidates and the limited supply of donor organs, it becomes increasingly important to identify individuals with the poorest prognoses.

Peak oxygen consumption (Vo$_2$) measured during maximal exercise testing provides an objective assessment of functional capacity in patients with heart failure and an indirect assessment of cardiovascular reserve. Previous studies have suggested that this measurement is a good short-term predictor of mortality. Moreover, a significant deterioration of maximal exercise performance frequently precedes...
clinal decompensation. Recent studies in patients with coronary artery disease and low ejection fraction suggest that exercise testing provides long-term prognostic information.

In the present study, we sought to investigate prospectively whether peak \( \text{VO}_2 \) can be used to identify ambulatory patients in whom cardiac transplantation can be safely deferred. All ambulatory patients referred for transplant underwent low-level exercise testing with measurement of oxygen consumption as well as measurement of resting ejection fraction and hemodynamic data. A peak \( \text{VO}_2 \) of 14 ml/kg/min or less (4 METS) was selected as a criterion for acceptance for cardiac transplant based on exercise data in the literature and on experience at our center in identifying patients with the most severe functional impairment. Candidates with low \( \text{VO}_2 \) (\( \leq 14 \) ml/kg/min) who were rejected for transplant for noncardiac reasons were selected as a control group from which to derive estimates of 1-year mortality without transplant. In the patients considered too well, serial exercise testing was performed, and cardiac transplantation was recommended if functional capacity deteriorated. We reasoned that if \( \text{VO}_2 \) was an adequate tool to time transplant, survival of patients followed in this manner would be high.

Methods

All ambulatory patients (\( n=122 \)) referred for cardiac transplantation evaluation to the Hospital of the University of Pennsylvania between October 1986 and December 1989 were included in the study. Patients dependent on inotropic or mechanical support were excluded. The average age of the 103 men and 19 women screened was 50±11 years (range, 22–69 years). Etiology of heart failure was coronary artery disease in 46% and dilated cardiomyopathy in 54%. Determination of NYHA class was performed by two authors at the time of initial evaluation. Thirteen percent were in NYHA class IV heart failure, 70% were in class III, and 17% were in class II.

Ejection fraction was obtained from radionuclide angiography and/or cardiac catheterization during the initial evaluation. Hemodynamic data were derived from Swan-Ganz catheterization performed with patients on their chronic medical regimens. Cardiac outputs were measured by thermodilution. Maximal treadmill exercise testing with respiratory gases was performed using the modified Naughton protocol. Measurements of mixed expired oxygen, mixed expired carbon dioxide, and expired volume were determined at rest and every 30 seconds throughout exercise using a metabolic cart (Sensor-Medics, Anaheim, Calif.). Anaerobic threshold was defined as 1) the point at which the ventilatory equivalent for \( \text{O}_2 \) (\( V_e/\text{VO}_2 \)) was minimal followed by a progressive increase; 2) the point after which the respiratory gas exchange ratio consistently exceeded the resting respiratory gas exchange ratio; and 3) the \( \text{VO}_2 \) after which a nonlinear increase in minute ventilation occurred relative to \( \text{VO}_2 \). Peak \( \text{VO}_2 \) of 14 ml/kg/min or less with attainment of anaerobic threshold was chosen as a criterion for acceptance as a transplant candidate. Exercise testing was not performed in candidates with severe angina and documented severe coronary artery disease (\( n=5 \)). Patients with \( \text{VO}_2 \) of 14 ml/kg/min or less who were not limited by angina and who failed to reach anaerobic threshold underwent repeat exercise testing. If on repeat testing anaerobic threshold was not achieved, the patient was excluded from study; only one patient was excluded for this reason.

Patients were divided into three categories: Group 1 comprised candidates accepted for transplantation; group 2 comprised candidates rejected for transplantation due to preserved exercise capacity; and group 3 comprised candidates with low peak \( \text{VO}_2 \) rejected for transplantation due to noncardiac reasons. Candidates with preserved exercise capacity underwent exercise tests every 3–6 months. Deterioration of exercise capacity to a peak \( \text{VO}_2 \) of 14 ml/kg/min or less resulted in crossover to group 1. Similarly, symptomatic improvement with objective evidence on exercise testing (i.e., \( \text{VO}_2 > 14 \) ml/kg/min) resulted in deactivation from the transplant list and crossover to group 2.

The majority of patients (\( n=100 \)) were followed in the Heart Failure Clinic of the Hospital of the University of Pennsylvania. Diuretic and vasodilator therapies were maximized. All patients were treated with digoxin and diuretics. Only two patients were not receiving vasodilators. All but five patients were treated with angiotensin converting enzyme inhibitors. Thirteen patients received investigational inotropic agents (all phosphodiesterase type III inhibitors). Only patients with symptomatic atrial or ventricular arrhythmias were treated with antiarrhythmic therapy (\( n=10 \)). One patient underwent implantation of an automatic defibrillator.

Follow-up of patients managed primarily outside the clinic system was determined by telephone interview of referring physicians and/or patients. Deaths occurring out of hospital within 24 hours and without relation to symptomatic deterioration were considered “sudden.” The deaths of patients with progressive symptomatic and/or hemodynamic deterioration were classified as resulting from progressive heart failure.

Statistical Analysis

Differences in characteristics among patient groups were compared by analysis of variance or \( \chi^2 \) analysis. Differences in characteristics within a patient group were compared by nonpaired \( t \) testing. Probability of survival from the time of initial evaluation was analyzed by the life-table method. Survival curves were compared using the log-rank test and Wilcoxon analysis. Cardiac transplantation was considered a censored observation (i.e., withdrawn from study at the time of transplant). Patients who crossed over into an alternate group were included in the groups to which they were originally assigned.
The association of individual variable with survival was obtained by univariate analysis (Wilcoxon and log rank). Examined variables were age, functional class, sex, etiology, pulmonary capillary wedge, cardiac index, and peak Vo2. Multivariate analysis was also performed using the Cox proportional hazards model. The relation among variables was examined by linear regression analysis. A probability value of less than 0.05 was considered significant. All data are expressed as mean±SD.

Results

Clinical Characteristics

Clinical characteristics of the 122 ambulatory patients screened for transplant are outlined in Table 1. A total of 116 baseline exercise tests were performed. In five patients, exercise testing was not conducted due to severe angina. One patient refused exercise testing. One patient with Vo2 of less than 14 ml/kg/min failed to reach anaerobic threshold in the absence of angina. Only one adverse event occurred during exercise testing; one patient developed a hemodynamically tolerated wide complex tachycardia that resolved spontaneously.

Forty patients were accepted for transplantation (group 1). Only one patient with a normal Vo2 was offered transplantation due to persistent severe resting symptoms; this patient was excluded from statistical analysis. Exercise testing was not performed in four patients due to severe angina. These patients were not included in survival analysis. Therefore, 35 patients comprised group 1. Two patients with aggressive diuretic and vasodilator therapy underwent marked symptomatic improvement with concomitant improvement in exercise performance. In these two patients, peak Vo2 increased from 8±4 to 19±6 ml/kg/min. Both patients crossed over into group 2 at 3 months after initial evaluation.

Fifty-two patients were considered too well for transplant on the basis of exercise data (group 2). In 44 of the patients, serial exercise tests were performed. Deterioration of exercise capacity occurred in four patients who crossed over into group 1 at a mean of 7±4 months after initial evaluation. In these four patients, peak Vo2 decreased from 16.1±0.3 to 12.0±0.7 ml/kg/min.

Twenty-seven candidates with reduced exercise capacity rejected for transplantation for noncardiac reasons composed group 3. Patients were denied transplantation due to advanced age (n=6), psychosocial problems (n=11), chronic obstructive lung disease (n=2), diabetes (n=2), past history of malignancy (n=2), elevated fixed pulmonary vascular resistance (n=1), and renal insufficiency (n=1). Two candidates refused transplant.

The clinical characteristics of the three groups are tabulated in Table 1 and Figure 1. Candidates with preserved exercise capacity (group 2) were comparable to candidates accepted for transplant (group 1) in regard to age, sex, etiology, NYHA class, ejection fraction, and cardiac index (p=NS for all). Pulmonary capillary wedge was significantly lower in group 2 than in group 1, although there was wide overlap. Candidates accepted (group 1) and rejected (group 3) for transplant were similar for all analyzed variables (p=NS for all).
Mancini et al  Exercise Capacity and Selection of Transplant Candidates

Survival

Cumulative survival is depicted in Figure 2. Patients with preserved exercise capacity (group 2) had 1- and 2-year survival rates of 94% and 84%, respectively. Patients accepted (group 1) and rejected (group 3) for transplant had similar survival (p=NS). The 1-year survival rate for patients accepted for transplant (group 1) was 70%. This survival is probably an overestimation of the survival of such patients because patients were removed from survival curve analysis by transplantation. For example, seven patients ultimately required inotropic and/or mechanical support before successful transplantation. Without transplantation, these patients probably would have died. Statistical analysis for group 1 patients with the seven patients requiring urgent transplantation viewed as deaths rather than as censored data points yields a 1-year actuarial survival rate of 48%. The 1- and 2-year survival rates for patients denied transplant (group 3) were 47% and 32% with a median survival of 11±3 months. The survival rates for both groups 1 and 3 were significantly less than for group 2 (p<0.005).

The 1- and 2-year survival rates for the 24 patients in group 1 who underwent cardiac transplantation were 83% and 76%, respectively. This survival is not...
Table 2. Clinical Outcome

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n)</th>
<th>Group 2 (n)</th>
<th>Group 3 (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths before transplant</td>
<td>6</td>
<td>5</td>
<td>14</td>
</tr>
<tr>
<td>Sudden death</td>
<td>3</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Progressive CHF</td>
<td>3</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Crossovers</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Group 1 to 2</td>
<td>2</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Group 2 to 1</td>
<td>...</td>
<td>4</td>
<td>...</td>
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<tr>
<td>Deaths in crossover</td>
<td>...</td>
<td>1</td>
<td>...</td>
</tr>
<tr>
<td>Transplants</td>
<td>24</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Deaths after transplant</td>
<td>3</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Total deaths</td>
<td>9</td>
<td>6</td>
<td>14</td>
</tr>
<tr>
<td>Deaths and transplants</td>
<td>33</td>
<td>10</td>
<td>15</td>
</tr>
</tbody>
</table>

CHF, congestive heart failure.

Table 3. Clinical Characteristics of Nonsurvivors

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths (n)</td>
<td>6</td>
<td>6</td>
<td>14</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>43±12</td>
<td>46±7</td>
<td>51±11</td>
</tr>
<tr>
<td>NYHA class (mean±SEM)</td>
<td>3.0</td>
<td>2.7±0.5*</td>
<td>3.5±0.5</td>
</tr>
<tr>
<td>Sex (n)</td>
<td>4</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Female</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Etiology (n)</td>
<td>CAD</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>DC</td>
<td>2</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>EF (%)</td>
<td>17±4</td>
<td>19±6</td>
<td>16±6.0</td>
</tr>
<tr>
<td>VO2 (ml/kg/min)</td>
<td>10.6±4.3</td>
<td>20±5.5†</td>
<td>10.1±3.0</td>
</tr>
<tr>
<td>PCW (mm Hg)</td>
<td>23±8</td>
<td>21±10*</td>
<td>30±9</td>
</tr>
<tr>
<td>CI (l/min/m²)</td>
<td>1.8±0.3</td>
<td>2.0±0.4</td>
<td>2.0±0.6</td>
</tr>
<tr>
<td>Mode (n)</td>
<td>CHF</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Sudden death</td>
<td>3</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Duration of follow-up (mo)</td>
<td>4±3†</td>
<td>15±8*†</td>
<td>7±4</td>
</tr>
</tbody>
</table>

NYHA class, New York Heart Association classification; CAD, coronary artery disease; DC, dilated cardiomyopathy; EF, ejection fraction; PCW, pulmonary capillary wedge; CI, cardiac index; CHF, congestive heart failure.

* p<0.05 group 2 versus group 3.
† p<0.05 group 1 versus group 2.
‡ p<0.05 group 1 versus group 3.

statistically different than the survival of group 2 patients (p=0.12) and is illustrated in Figure 3.

Clinical outcome of the three groups is outlined in Table 2. All deaths in the group with peak VO2 of more than 14 ml/kg/min (group 2) resulted from sudden death. Of the four patients whose exercise capacity deteriorated, all were successfully transplanted 10±6 months after crossover into group 1. Of the two patients deactivated from the transplant list, one remains in functional class 1 at 30 months after crossover. The other patient died from a sudden death episode 22 months after crossover. Cardiac transplantation was performed in one patient in group 3 at an alternate transplant center.

Clinical characteristics of the nonsurvivors are summarized in Table 3. Peak VO2 was significantly higher, pulmonary capillary wedge was slightly lower, and duration of follow-up was significantly greater in group 2 nonsurvivors. Comparison of the survivors and nonsurvivors of groups 2 and 3 were performed (Table 4). Nonsurvivors were defined as patients who died, who were transplanted, and/or who crossed over into group 1. There were no statistically significant differences in any of the analyzed variables for group 2. Comparison of group 3 survivors and nonsurvivors also demonstrated no significant differences in age, ejection fraction, and VO2. Pulmonary capillary wedge tended to be higher and cardiac index was lower in nonsurvivors, but neither achieved statistical significance. However, NYHA class was significantly higher in nonsurvivors.

Univariate and Multivariate Analyses

Results of univariate (log rank) and multivariate analyses are tabulated in Table 5. By both univariate and multivariate analysis, only peak VO2 and pulmonary capillary wedge were significant predictors. Because eight variables were analyzed, a rigid multivariate analysis would require a probability value of less than 0.00625 as a maximum for significance. At this level, only peak VO2 achieved significance. Proportional hazards analysis was performed with patients divided into two groups by pulmonary capillary wedge (i.e., >15 and ≤15 mm Hg). This variable (PCW HL) offered no prognostic value.

Table 4. Comparison of Survivors and Nonsurvivors in Groups 2 and 3

<table>
<thead>
<tr>
<th></th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>50±9</td>
<td>52±11</td>
</tr>
<tr>
<td>NYHA class</td>
<td>2.8±0.4</td>
<td>3.0±0.6</td>
</tr>
<tr>
<td>EF (%)</td>
<td>19±5</td>
<td>20±8</td>
</tr>
<tr>
<td>VO2 (ml/kg/min)</td>
<td>17.5±3.7</td>
<td>19.4±3.9</td>
</tr>
<tr>
<td>PCW (mm Hg)</td>
<td>21±8</td>
<td>18±10</td>
</tr>
<tr>
<td>CI (l/min/m²)</td>
<td>2.0±0.3</td>
<td>2.1±0.5</td>
</tr>
<tr>
<td>Duration of follow-up (mo)</td>
<td>15±7</td>
<td>14±9</td>
</tr>
</tbody>
</table>

*Survivor versus nonsurvivor.
NYHA class, New York Heart Association classification; EF, ejection fraction; PCW, pulmonary capillary wedge; CI, cardiac index.
TABLE 5. Univariate and Multivariate Analyses

<table>
<thead>
<tr>
<th>Prognostic factor</th>
<th>Univariate analysis $p$</th>
<th>Multivariate analysis $p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak VO$_2$</td>
<td>0.002</td>
<td>0.003</td>
</tr>
<tr>
<td>PCW</td>
<td>0.003</td>
<td>0.04</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.08</td>
<td>0.34</td>
</tr>
<tr>
<td>CI</td>
<td>0.08</td>
<td>0.89</td>
</tr>
<tr>
<td>Etiology</td>
<td>0.39</td>
<td>0.39</td>
</tr>
<tr>
<td>Age</td>
<td>0.46</td>
<td>0.06</td>
</tr>
<tr>
<td>Sex</td>
<td>0.52</td>
<td>0.09</td>
</tr>
<tr>
<td>NYHA class</td>
<td>0.95</td>
<td>0.72</td>
</tr>
<tr>
<td>PCW HL</td>
<td>. . .</td>
<td>0.10</td>
</tr>
</tbody>
</table>

PCW, pulmonary capillary wedge; LVEF, left ventricular ejection fraction; CI, cardiac index; NYHA class, New York Heart Association classification; PCW HL, pulmonary capillary wedge above and less than or equal to 15 mm Hg (see text).

The 1-year survival curves were derived with subdivisions of VO$_2$, ejection fraction, and pulmonary capillary wedge. Patients were divided into the following groups—VO$_2$: 10 or less, more than 10 through 14, more than 14 through 18, more than 18 ml/kg/min; ejection fraction: 10% or less, more than 10% and less than 20%, equal to or more than 20%; pulmonary capillary wedge: 10 or less, more than 10 through 15, more than 15 through 20, more than 20 mm Hg. Transplant was treated as a censored observation. Results are represented in Figure 4. Patients with a VO$_2$ of 10 ml/kg/min or less had significantly reduced survival rates compared with patients with VO$_2$ of more than 14 ml/kg/min. Survival in patients with VO$_2$ of more than 14 ml/kg/min was comparable to survival after transplantation. Although survival tended to improve with increasing ejection fraction and decreasing pulmonary capillary wedge, no statistically significant differences were detected among subgroups.

Linear regression analysis was performed using peak VO$_2$ versus NYHA class, ejection fraction, pulmonary capillary wedge pressure, and cardiac index. No statistically significant relations were demonstrated ($r=0.1$ to $-0.16; p=NS$). However, a weak negative linear correlation was observed between peak VO$_2$ and age ($r=-0.28; p<0.01$).

Discussion

In ambulatory patients with heart failure, selection criteria for cardiac transplantation has focused primarily on resting hemodynamic data and NYHA classification. However, a substantial percentage of patients with severe resting hemodynamic abnormalities may survive for extended periods. Moreover, NYHA classification as a measure of functional capacity is a subjective and frequently inaccurate index.

Exercise capacity as assessed by peak VO$_2$ is a dynamic objective variable that assesses cardiac reserve and peripheral adaptations to a reduced cardiac output much more accurately than NYHA classification. In general, previous studies have demonstrated the usefulness of peak VO$_2$ to risk-stratify patients with reduced left ventricular function. In a study of 27 patients, Szlachcic et al$^4$ described a 77% 1-year mortality rate for patients with VO$_2$ of 10 ml/kg/min or less and a 21% mortality rate for those with VO$_2$ of 10–18 ml/kg/min. Likoff et al$^7$ described a 36% 1-year mortality rate in 201 patients with heart failure, and VO$_2$ of less than 13 ml/kg/min compared with 15% when VO$_2$ exceeded 13 ml/kg/min. A recent report describes exercise capacity as an independent long-term prognostic indicator in patients with low ejection fraction after myocardial infarction.$^11$ In contrast, Franciosa et al$^{15,16}$...
failed to demonstrate the ability of maximal \( \dot{V}O_2 \) to predict survival during a 3-year period. In a report from the Captopril-Digoxin Research Group,17 treadmill exercise duration was not an independent predictor of mortality in 295 patients with mild-to-moderate heart failure. However, in that study, patients exercised for an average of almost 10 minutes, achieving a work load equal to 6 METS or \( \dot{V}O_2 \) of 21 ml/kg/min. At this exercise level, overall prognosis is good and an isolated measurement of \( \dot{V}O_2 \) cannot identify patients at risk for sudden death and/or progressive heart failure.

In the present study, we tested the hypothesis that peak \( \dot{V}O_2 \) could be used to identify ambulatory patients with heart failure in whom cardiac transplantation can be safely delayed. Specifically, we prospectively used a peak \( \dot{V}O_2 \) level of more than 14 ml/kg/min as an indicator of good prognosis. Patients with peak \( \dot{V}O_2 \) of more than 14 ml/kg/min were not referred for transplantation. Patients with peak \( \dot{V}O_2 \) of 14 ml/kg/min or less were offered transplantation, unless transplantation was contraindicated for noncardiac reasons. In patients denied transplantation, exercise testing was performed at 3–6-month intervals, and transplantation was offered if peak \( \dot{V}O_2 \) decreased to less than 14 ml/kg/min.

With this approach, we evaluated 122 patients. Forty-three percent of the patients were found to have a preserved exercise capacity. Ejection fraction, NYHA functional classification, and resting cardiac index of these patients did not differ significantly from those of patients accepted for transplant. This illustrates the known dissociation between exercise capacity and both resting hemodynamic variables and ejection fraction.3,4 The pulmonary wedge pressure was slightly but significantly lower in the patients with preserved exercise capacity, but there was substantial overlap between the groups. Previous studies have demonstrated that patients with preserved exercise capacity tend to have lower mean pulmonary pressures.18

Survival

Survival of the patients with a peak \( \dot{V}O_2 \) of more than 14 ml/kg/min was 94% at 1 year and 84% at 2 years. These survival rates are comparable if not better than survival achieved with cardiac transplantation.1 This good survival is not totally unexpected, as recent advances in the therapy of heart failure, specifically, initiation of vasodilator therapy, have resulted in improved survival.19–21 Patients rejected for transplant had a 1-year survival rate of 47%. Although this 1-year survival rate was considerably greater than previous reports of 21% in patients denied transplant for nonmedical criteria,22 our control group comprised only ambulatory patients. Moreover, it is consistent with the survival rates of patients with severe left ventricular dysfunction and reduced \( \dot{V}O_2 \).9

To determine whether other clinical and/or hemodynamic variables could have predicted clinical outcome as effectively as peak \( \dot{V}O_2 \), we used univariate and multivariate analyses to examine the relation of all measured variables to survival. It should be emphasized that this analysis entails a fundamental bias in favor of peak \( \dot{V}O_2 \) because this variable was used to guide therapy. Analysis identified only peak \( \dot{V}O_2 \) and pulmonary wedge pressure as significant predictors of survival, with peak \( \dot{V}O_2 \) providing the most prognostic information. In previous reports, elevated filling pressures have been variably shown to indicate a worse prognosis.23–27

We also sought to examine the validity of using a peak \( \dot{V}O_2 \) level of more than 14 ml/kg/min to identify patients in whom transplantation could be safely deferred. When the population was subdivided by different ranges of \( \dot{V}O_2 \) (Figure 3), a peak \( \dot{V}O_2 \) level of less than 10 ml/kg/min was associated with a significantly poorer survival, and a peak \( \dot{V}O_2 \) of more than 14 ml/kg/min was associated with survival comparable to survival after transplantation. Thus, this criterion appeared to provide a reasonable guideline.

In our patients considered too well for transplantation, no deaths resulted from progressive heart failure as deterioration in functional status transferred patients into group 1. Of the four patients whose exercise capacity deteriorated, all survived to be transplanted and all were ambulatory at the time of transplant. Thus, a decline in exercise capacity did not signal a precipitous deterioration but provided adequate time to await transplantation.

Clinical Implications

Our results suggest that measurement of peak exercise \( \dot{V}O_2 \) provides valuable prognostic information in patients with ambulatory heart failure. Patients with preserved exercise capacity despite severe resting hemodynamic impairment have survival and functional capacity equal to those afforded by cardiac transplantation.28 Based on our data, it appears that patients with preserved exercise capacity can be treated with medical therapy until exercise capacity deteriorates. At that time, transplantation can be undertaken.

This approach differs from prior criteria suggested by Stevenson et al.29 and Keogh et al.30 Stevenson et al described a 46% 1-year survival rate in 28 patients with idiopathic dilated cardiomyopathy considered too well for transplant. Based on this observation, it was recommended that patients with severe hemodynamic dysfunction be transplanted regardless of symptoms. However, no exercise testing was performed in this retrospective study, and medical therapy was not controlled. This may explain the difference between our results and those of Stevenson et al. Keogh et al observed a high mortality in patients with ejection fractions of less than 20% and proposed that all patients with such ejection fractions undergo transplantation regardless of symptoms or hemodynamic parameters. We also observed a strong trend favoring poorer survival in patients with ejection fractions of less than 20%. However, in our study peak \( \dot{V}O_2 \) was a better predictor of survival than
ejection fraction in patients with uniform reduction of ejection fraction.

The major threat to survival in patients with preserved exercise capacity was sudden death. This is consistent with recent findings of Stevenson et al. 28, 29 In a group of patients considered “too well” 29 and in a “medically stabilized” group, 28 these investigators noted that the incidence of sudden death was 82% and 90%, respectively. The major clinical challenge in the management of patients with preserved exercise capacity is the prevention of sudden death. Identification of prognostic indicators of sudden death followed by treatment with antiarrhythmics such as amiodarone 31, 32 or antitachycardia devices would be preferable to cardiac transplantation. Presently, there is no marker to identify those individuals at highest risk for sudden death. Only a small number of patients with heart failure who will die suddenly will have premonitory symptoms. 33 The presence of frequent complex ventricular ectopy or frequent nonsustained ventricular tachycardia on Holter monitor, 34, 35 the demonstration of late potentials on signal-averaged electrocardiograms, 36 and easy inducibility of sustained ventricular tachycardia during electrophysiological study 37, 38 have been variably reported as predictive of future fatal arrhythmic events. However, there is no current evidence that antiarrhythmic therapy can prevent sudden death.

Criticisms of Study

One major criticism of the present study is that we examined a heterogeneous group of patients on heterogeneous therapy at different stages in their disease processes, and we have focused on an isolated variable to guide medical versus surgical therapy. Several potentially important clinical variables such as the presence or absence of myocardial ischemia, single versus multivessel coronary artery disease, one versus multiple prior myocardial infarcts, and differences in renal function or electrolytes were not considered or analyzed. Nevertheless, despite the heterogeneity, hemodynamic measurements, ejection fraction, and other variables were remarkably similar when the groups were analyzed at the time of referral.

Another potential criticism is that in most patients only one baseline exercise test was performed. An improvement in exercise time and VO₂ at rest may occur with familiarization of the technique. 39 Thus, VO₂ at time of initial evaluation may be slightly lower than if serial baseline tests were performed. Nevertheless, this does not detract from the finding that an initial good exercise performance carries an excellent prognosis. Other potential limitations of peak VO₂ also must be considered. First, patients with heart failure seldom achieve a true maximum oxygen consumption. Second, although peak VO₂ is primarily determined by cardiovascular reserve, other factors such as local hormonal changes, age, and conditioning also affect maximal oxygen consumption.

Summary

We advocate routine determination of exercise capacity in all ambulatory patients with severe heart failure referred for cardiac transplantation. Stratification of ambulatory patients on the basis of exercise capacity can effectively identify patients with the poorest prognoses who should be selected for transplant. This approach may alleviate the ever-growing problem of scarcity of donor organs.

The precise definition used to define preserved exercise capacity is not entirely clear. Although a peak VO₂ of more than 14 ml/kg/min was used in the present study, this by no means represents an inflexible guideline. The ultimate decision to transplant should be based on multiple clinical parameters. This study simply emphasizes that one of these parameters should be measurement of peak exercise VO₂.

References


KEY WORDS: exercise • heart failure • transplantation
Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure.

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_Circulation_. 1991;83:778-786
doi: 10.1161/01.CIR.83.3.778

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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