Cardiopulmonary Exercise Testing Identifies Low Risk Patients With Heart Failure and Severely Impaired Exercise Capacity Considered for Heart Transplantation

NAOHIKO OSADA, MD, BERNARD R. CHAITMAN, MD, FACC, LESLIE W. MILLER, MD, FACC, DANIEL YIP, MD, MARY BETH CISHEK, MD, THOMAS L. WOLFORD, MD, THOMAS J. DONOHUE, MD, FACC
Saint Louis, Missouri

Objectives. The 3-year survival rates of 500 patients with congestive heart failure (CHF) referred for heart transplantation were assessed to evaluate the clinical and exercise variables most useful for estimating prognostic risk.

Background. Detailed prognostic risk stratification of patients with a peak exercise oxygen consumption (VO2) ≤14 ml/min per kg to identify lower risk patient subsets has been limited in earlier series by relatively small sample size.

Methods. Cardiopulmonary exercise testing was performed in 500 patients with CHF referred for heart transplantation; 154 (31%) had a peak exercise VO2 ≤14 ml/min per kg. Univariate and multivariate analyses were performed to identify the 3-year prognostic risk.

Results. The 55% 3-year survival rate of the 77 patients with a peak exercise VO2 ≤14 ml/min per kg unable to reach a peak exercise systolic blood pressure (SBP) of 120 mm Hg was significantly lower than the 83% survival rate in the 74 patients able to reach this exercise blood pressure (p = 0.004). Multivariate analysis revealed that peak exercise SBP (p = 0.0005) and percent predicted peak VO2 ≤50% (p = 0.04) were the two most important predictors for the combined end point of death or listing as Status 1.

Conclusions. Peak exercise SBP and percent predicted peak exercise VO2 are two inexpensive and easily measured noninvasive variables that can be used to further prognostically risk stratify ambulatory patients with CHF referred for heart transplantation with a peak exercise VO2 ≤14 ml/min per kg.

(J Am Coll Cardiol 1998;31:577–82) ©1998 by the American College of Cardiology

The decision to list ambulatory patients with congestive heart failure (CHF) for heart transplantation is difficult, and objective measurements for identifying patients most likely to benefit from the procedure are highly desirable. In a recent American Heart Association consensus document, clinical, hemodynamic, functional capacity, neurohumoral and arrhythmia variables were defined to optimize evaluation, treatment and selection of candidates for heart transplantation (1). Exercise testing with respiratory gas analyses is a standardized approach for objectively documenting functional capacity and is a more reliable measurement than exercise duration (2). Mancini et al. (3), Stelken et al. (4) and others (5–8) in observational reports have demonstrated that the short-term prognosis of patients with a peak oxygen consumption (VO2) ≤14 ml/min per kg is markedly impaired (5–8) compared with heart transplant recipients followed up for a similar duration (3,4).

Exercise capacity is determined in part by the ability to increase cardiac output and extract oxygen peripherally and by muscle conditioning, motivation, age, gender and pulmonary status. The multifactorial control of variables that influence peak exercise capacity may explain in part why some patients with CHF and limited exercise capacity (peak exercise VO2 ≤14 ml/min per kg) have a favorable prognosis and may be treated with continued medical therapy rather than heart transplantation (9–17). Stevenson et al. (10) reported the outcome of 68 of 107 patients listed for heart transplantation with an initial peak VO2 ≤14 ml/min per kg. After 6 months of optimizing medical management, 38 patients increased peak VO2, and 31 were taken off the active waiting list; their subsequent 2-year survival rate was 100%. Thus, in addition to the standard variables used to estimate prognosis in patients with CHF, such as duration of symptoms, presence of obstructive coronary disease, New York Heart Association functional class, pulmonary artery systolic pressure and gender, additional

From the Division of Cardiology, Department of Medicine, Saint Louis University School of Medicine, Saint Louis, Missouri. This study was supported in part by a grant from the Lichtenstein Foundation, Saint Louis, Missouri. Manuscript received June 3, 1997; revised manuscript received November 20, 1997, accepted November 21, 1997.

Address for correspondence: Dr. Bernard R. Chaitman, Saint Louis University Health Care Sciences Center, Division of Cardiology, 3635 Vista Avenue at Grand Boulevard, PO Box 15250, Saint Louis, Missouri 63110-0250. E-mail: chaitman@slu.edu.

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criteria to optimally select the highest risk patients with a peak exercise V\textsubscript{O2} \leq 14 ml/min per kg would be of benefit. In many earlier reports (3–7), the number of patients with a peak V\textsubscript{O2} \leq 14 ml/min per kg was insufficient to study this particular subset in detail. The aim of the present report is to examine the use of cardiopulmonary exercise testing in risk stratification of 500 patients with CHF referred for heart transplantation evaluation. Specifically, we tested the hypothesis that clinical variables, exercise hemodynamic response and adjustment of peak V\textsubscript{O2} for age, gender and weight would optimize mortality estimates in the \sim 30\% of patients with CHF and a peak V\textsubscript{O2} \leq 14 ml/min per kg referred for heart transplantation evaluation.

### Methods

#### Patients.

The study included 500 consecutive ambulatory patients with CHF referred to the Saint Louis University Heart Failure Service and who performed cardiopulmonary exercise testing between March 1991 and April 1996. The consecutive series includes 176 patients previously described (4). The mean (±SD) age was 50 ± 10 years (range 19 to 80); 79\% were men, and most patients were in functional class III. The etiology of heart failure was ischemic heart disease in 238 patients and dilated cardiomyopathy in 262. At the time of initial evaluation, 114 patients (23\%) were listed for heart transplantation, and 72 (14\%) ultimately underwent heart transplantation during follow-up. Of the 500 patients, 154 (31\%) had a peak exercise V\textsubscript{O2} \leq 14 ml/min per kg; their clinical characteristics are shown in Table 1.

#### Cardiopulmonary exercise testing.

A symptom-limited cardiopulmonary exercise test was performed after written informed consent was obtained. The modified Bruce protocol was used in 185 patients (37\%) and the Asymptomatic Cardiac Ischemia Pilot (ACIP) or modified Naughton protocol in 315 (63\%) (18). Heart rate, blood pressure and a 12-lead electrocardiogram were obtained at rest, at each exercise stage and for 5 min in the postexercise phase. Respiratory gas analysis was measured using a Medical Graphics System, as previously described (4). Oxygen consumption (V\textsubscript{O2}), carbon dioxide production (V\textsubscript{CO2}), minute ventilation (V\textsubscript{E}), breathing rate, respiratory rate exchange ratio and ventilatory equivalents for O\textsubscript{2} (Ve/V\textsubscript{O2}) and CO\textsubscript{2} (Ve/V\textsubscript{CO2}) were measured continuously using a moving average for eight breaths. Peak V\textsubscript{O2} was defined as the highest V\textsubscript{O2} observed during the exercise test. Age-, gender- and weight-adjusted predicted V\textsubscript{O2} values were determined using the Wassermann formulas (19). The anaerobic threshold was defined as the point at which the lactate concentration in the blood increased during exercise while the V\textsubscript{O2} increased at a progressively lower rate. The RER was defined as 1.10 for anaerobic threshold. These data were used as the basis for determining the amount of exercise required to reach the anaerobic threshold.

### Table 1. Clinical and Exercise Characteristics of 154 Patients With Marked Impairment of Exercise Capacity (peak oxygen uptake \leq 14 ml/min per kg)

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Survivors</th>
<th>Nonsurvivors</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>52 ± 11</td>
<td>53 ± 11</td>
<td>50 ± 12</td>
<td>0.23</td>
</tr>
<tr>
<td>Male</td>
<td>75%</td>
<td>72%</td>
<td>83%</td>
<td>0.1</td>
</tr>
<tr>
<td>Ischemic cardiomyopathy</td>
<td>55%</td>
<td>56%</td>
<td>46%</td>
<td>0.87</td>
</tr>
<tr>
<td>Hypertension</td>
<td>45%</td>
<td>49%</td>
<td>31%</td>
<td>0.06</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>20%</td>
<td>21%</td>
<td>17%</td>
<td>0.38</td>
</tr>
<tr>
<td>Smoking</td>
<td>49%</td>
<td>48%</td>
<td>63%</td>
<td>0.6</td>
</tr>
<tr>
<td>ACE inhibitor therapy</td>
<td>87%</td>
<td>86%</td>
<td>91%</td>
<td>0.37</td>
</tr>
<tr>
<td>Digitalis usage</td>
<td>73%</td>
<td>70%</td>
<td>86%</td>
<td>0.06</td>
</tr>
<tr>
<td>Diuretic usage</td>
<td>82%</td>
<td>79%</td>
<td>94%</td>
<td>0.04</td>
</tr>
<tr>
<td>Mean LVEF (%) (n = 57)</td>
<td>24 ± 9</td>
<td>24 ± 10</td>
<td>23 ± 8</td>
<td>0.5</td>
</tr>
<tr>
<td>Exercise variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest HR (beats/min)</td>
<td>95 ± 17</td>
<td>94 ± 17</td>
<td>98 ± 16</td>
<td>0.17</td>
</tr>
<tr>
<td>Peak exercise HR (beats/min)</td>
<td>130 ± 21</td>
<td>131 ± 22</td>
<td>129 ± 19</td>
<td>0.7</td>
</tr>
<tr>
<td>Peak rest HR (beats/min)</td>
<td>35 ± 18</td>
<td>54 ± 24</td>
<td>37 ± 20</td>
<td>0.001</td>
</tr>
<tr>
<td>Peak exercise SBP (mm Hg)</td>
<td>127 ± 30</td>
<td>131 ± 30</td>
<td>114 ± 25</td>
<td>0.002</td>
</tr>
<tr>
<td>Peak exercise RER</td>
<td>1.11 ± 0.2</td>
<td>1.15 ± 0.2</td>
<td>1.15 ± 0.16</td>
<td>0.26</td>
</tr>
<tr>
<td>Peak Ve (liters/min)</td>
<td>51 ± 18</td>
<td>49 ± 19</td>
<td>56 ± 17</td>
<td>0.05</td>
</tr>
<tr>
<td>MVV (liters/min)</td>
<td>97 ± 32</td>
<td>95 ± 32</td>
<td>104 ± 31</td>
<td>0.12</td>
</tr>
<tr>
<td>Peak V\textsubscript{O2} (ml/min per kg)</td>
<td>12 ± 2</td>
<td>11.5 ± 1.9</td>
<td>11.5 ± 1.8</td>
<td>0.97</td>
</tr>
<tr>
<td>% predicted peak V\textsubscript{O2}</td>
<td>44 ± 16</td>
<td>45 ± 17</td>
<td>39 ± 11</td>
<td>0.04</td>
</tr>
<tr>
<td>Anaerobic threshold (ml/min per kg) (n = 350)</td>
<td>9 ± 1</td>
<td>9 ± 1</td>
<td>9 ± 2</td>
<td>0.81</td>
</tr>
</tbody>
</table>

Data presented are mean value ± SD or percent of patients. ACE = angiotensin converting enzyme; HR = heart rate; LVEF = left ventricular ejection fraction by contrast left ventriculography; MVV = maximal ventilatory volume; RER = respiratory exchange ratio; SBP = systolic blood pressure; Ve = minute ventilation; V\textsubscript{O2} = oxygen consumption.
obic threshold was determined in the last consecutive 350 patients using the V-slope method (20). Of the 500 patients, 422 (84%) stopped exercise because of either dyspnea or excessive fatigue.

**Follow-up.** All patients were followed-up prospectively at the Saint Louis University Heart Failure clinic. The average duration of follow-up was 25 ± 17 months (range 0.2 to 64.5). Cardiac end points were defined as death or admission to the intensive care unit for prolonged inotropic or mechanical cardiovascular support, leading to Status 1 listing for heart transplantation. During follow-up, 56 patients died, and 72 patients underwent heart transplantation.

**Statistical analysis.** Univariate analysis of baseline clinical and exercise variables was performed for the end point of death or cardiac event (death or change to Status 1 transplant priority). Results are expressed as mean value ± SD. Inter-group differences between clinical or exercise variables were compared using an unpaired t test or chi-square analysis, where appropriate. To account for multiple subgroup comparisons, p = 0.01 was regarded as showing some evidence against the null hypothesis and p = 0.001 as strong evidence.

Survival estimates were calculated using the Kaplan-Meier method (21). Differences between survival estimates were compared using the log-rank test (22). Cox proportional hazard analyses were used to measure the impact of clinical history and cardiopulmonary exercise test results on cardiac events (23). Separate analyses were performed for the end point of death or cardiac event (death or change to Status 1 transplant priority).

**Results**

The average peak VO$_2$ of the study group was 17.3 ± 5.7 ml/min per kg (60.7 ± 21.6% predicted peak VO$_2$). Of the 500 patients, 34, 120 and 346 reached a peak VO$_2$ ≤10, >10 to 14 and >14 ml/min per kg, respectively. Univariate predictors of mortality included a greater rest heart rate (p = 0.0008) and a lower peak exercise heart rate (p = 0.01), SBP (p < 0.0001), peak exercise VO$_2$ (p < 0.0001), percent predicted VO$_2$ (p < 0.0001) and anaerobic threshold (p < 0.0001).

Independent predictors of death by multivariate analysis were peak VO$_2$ ≤14 ml/min per kg (p < 0.0001), peak exercise SBP ≤120 mm Hg (p < 0.0001), rest heart rate >100 beats/min (p < 0.003) and male gender (p = 0.003). When multivariate analysis was performed for the combined end point of death or listing as Status 1, peak exercise VO$_2$ ≤14 ml/min per kg (p = 0.002), peak exercise SBP ≤14 ml/min per kg (p < 0.0001) and rest heart rate >100 beats/min (p < 0.0001) were selected as independent predictors.

**Patients with marked impairment of exercise capacity (peak exercise VO$_2$ ≤14 ml/min per kg).** Clinical and exercise variables to predict death were examined by univariate analysis in the 154 patients with a peak VO$_2$ ≤14 ml/min per kg (Table 1). Peak exercise SBP <120 mm Hg (p = 0.002) was the only variable that was a significant predictor of death. Peak exercise SBP (p = 0.004), percent predicted peak VO$_2$ (p = 0.002), male gender (p = 0.02) and rest heart rate (p = 0.03) were the only significant univariate predictors of the combined end point of death or change to Status 1 transplant priority.

Multivariate analysis revealed that peak exercise SBP was the single most important variable for death (p = 0.0005), and for the combined end point, peak exercise SBP (p = 0.0005) and percent predicted peak VO$_2$ ≤50% (p = 0.04) were the only two variables selected (Table 2).

**Three-year survival estimates.** The 3-year survival rate was 93 ± 2%, 68 ± 5% and 75 ± 9% for patients with a peak VO$_2$ >14, >10 to 14 and ≤10 ml/min per kg, respectively (Fig. 1). The difference between patients with a peak VO$_2$ >14 and ≤14 ml/min per kg was statistically significant (p < 0.0001). There was no significant difference between patients in whom peak exercise capacity was >10 to 14 and ≤10 ml/min per kg.

When patients were stratified according to percent predicted peak VO$_2$, the 3-year survival rate was 93 ± 2%, 77 ± 5% and 57 ± 10%, respectively (Fig. 2). The difference between patients who achieved a percent predicted peak VO$_2$ >50%, >35% to 50% and ≤35% was statistically significant (p < 0.0001).

The 154 patients with a peak exercise VO$_2$ ≤14 ml/min per kg were stratified according to percent predicted peak VO$_2$ >50% (n = 44), and ≤50% (n = 110) (Fig. 3). The 91 ± 5% 3-year survival rate of patients with a peak VO$_2$ ≤14 ml/min per kg able to achieve a percent predicted peak VO$_2$ >50% was
similar to the 93 ± 2% survival rate of patients initially able to achieve a peak exercise VO₂ >14 ml/min per kg. However, the 61 ± 5% 3-year survival rate in patients with a peak exercise VO₂ ≤14 ml/min per kg and a percent predicted peak VO₂ ≤50% was associated with a significantly worse 3-year survival rate (p = 0.0009). The results were similar for the combined end point of cardiac death or listing as Status 1.

Exercise SBP. The 3-year survival estimates of patients with a peak VO₂ ≤14 ml/min per kg were examined in patients able to reach a peak exercise SBP >120 mm Hg and ≤120 mm Hg (Fig. 4). In patients with a peak VO₂ ≤14 ml/min per kg, the 55% 3-year survival rate of the 77 patients unable to reach a peak exercise SBP of 120 mm Hg was significantly worse than the 83% survival rate in the 74 patients able to reach this exercise SBP (p = 0.004). Exercise SBP measurements were not available for three patients. The 83% 3-year survival rate in patients with a peak VO₂ ≤14 ml/min per kg and a peak exercise SBP >120 mm Hg was significantly lower than that of the 346 patients with a peak VO₂ >14 ml/min per kg (p = 0.02).

Gender. In the 346 patients with a peak VO₂ >14 ml/min per kg, the 3-year survival rate was 100% in women and 92 ± 2% in men (p = 0.07). The 3-year survival rate in the 154 patients with a peak VO₂ ≤14 ml/min per kg was 82 ± 7% in women and 65 ± 6% in men (p = 0.08).

Univariate and multivariate analyses of the 105 women in the study cohort revealed that the percent predicted peak VO₂ was the best independent predictor of survival free of cardiac events. However, the number of events was relatively small; seven women died before heart transplantation, and an additional four patients were listed as Status 1.

Of the 44 patients with a peak VO₂ ≤14 ml/min per kg with a percent predicted peak VO₂ >50% (Fig. 3), 32 were women (73%). Of the 110 patients with a peak VO₂ ≤14 ml/min per kg with a percent predicted peak VO₂ ≤50%, 7 were women (6%) (p < 0.001). There were no significant gender differences with regard to age.

Discussion

The use of cardiopulmonary exercise testing as an objective measure for estimating prognosis in ambulatory patients with CHF is well established (1–8). The prognostic risk significantly increases when the peak VO₂ decreases to <14 ml/min per kg. In our 154 patients with a peak VO₂ ≤14 ml/min per kg, we did not find a significant difference in 3-year survival rates between patients with a peak VO₂ >10 to 14 and ≤10 ml/min per kg, confirming the findings of Mancini et al. (3). The 93% 3-year survival rate in our 346 patients with a peak exercise VO₂ >14 ml/min per kg is consistent with earlier reports (3–8).

Chomsky et al. (15) evaluated cardiopulmonary and hemodynamic exercise responses of 185 ambulatory patients with CHF and a mean peak VO₂ of 12.9 ml/min per kg referred for...
heart transplantation. The 1-year survival estimates were significantly improved by measuring exercise cardiac output rather than peak exercise VO₂ alone. In multivariate analysis, a peak exercise VO₂ <10 ml/min per kg identified a high risk patient subset. Mancini et al. (14), in a 65 patient series with a mean peak VO₂ of 12.1 ml/min per kg, reported only a minimal improvement in risk prognostication when exercise cardiac output measurements were added to noninvasive cardiopulmonary exercise testing after an average follow-up of 232 days. The addition of right heart catheterization to cardiopulmonary exercise testing when evaluating ambulatory patients with CHF increases costs and exposes the patient to a minor risk. If similar results can be achieved by adjusting peak VO₂ measurements for age, gender and weight and assessment of peak exercise SBP, it would be a more cost-effective approach. Our study differs from the earlier reports in that exercise hemodynamic measurements were not made, and the duration of follow-up was 3 years rather than 1 year. The average peak VO₂ in our 154 patients with a peak VO₂ ≤14 ml/min per kg was 12 ± 2 ml/min per kg, similar to the patients studied by Chomsky et al. (15) and Mancini et al. (14).

In our patients with a peak VO₂ ≤14 ml/min per kg, peak exercise SBP and percent predicted peak VO₂ were important variables useful in further stratifying prognostic risk. The data indicate that in patients with a peak VO₂ ≤14 ml/min per kg, the ability to achieve a predicted peak VO₂ >50% is associated with a 3-year survival rate similar to patients able to achieve a peak VO₂ >14 ml/min per kg (15). The 3-year survival rate of 61 ± 6% in patients unable to reach 50% predicted peak VO₂ identified a patient subset, predominantly male, in whom heart transplantation would be expected to result in an improved survival benefit. In the subset of patients with a peak VO₂ ≤14 ml/min per kg, inability to achieve a peak exercise SBP of 120 mm Hg also identified a prognostic high risk patient subset with an unfavorable 3-year survival rate (55 ± 7%). The cutpoint of 120 mm Hg for exercise SBP was chosen because the average exercise SBP in patients with a peak VO₂ <14 ml/min per kg was 124 mm Hg in our series. The relation between the inability to adequately augment exercise SBP and an adverse prognosis has been reported by others, although in some series peak exercise SBP has not been found to be predictive of mortality (8,24,25).

In a previous report from our laboratory (4), percent predicted peak VO₂ was found to be a more useful predictor of 1-year outcome than peak VO₂ alone. In the earlier report, the average peak VO₂ was 16.3 ml/min per kg in the 181 patients with CHF, in contrast to the 17.3 ml/min per kg in our current 500-patient series with a longer duration of follow-up. These differences may explain in part why percent predicted peak VO₂ was predictive of outcome only in the subset of patients in our current series with a peak VO₂ <14 ml/min per kg. We chose the Wassermann formula to derive the percent predicted VO₂ in both reports; other equations can also be used to derive this variable (4). Osada et al. (26) reported that the greatest magnitude of increase in peak VO₂ after heart transplant is in a subset of patients with the lowest preoperative percent predicted peak VO₂. Aaronson and Mancini (11) examined percent predicted maximal VO₂ and peak exercise consumption in 272 ambulatory patients with CHF referred for heart transplantation. The performance of peak exercise VO₂, corrected for body weight was similar to that of weight-normalized peak VO₂. In univariate hazard analysis, percent predicted VO₂ with the Wassermann formula was the single best predictor of patient survival, with the predominant improvement in survival estimates occurring in women. Adams et al. (27) reported a significantly better survival rate in women than in men with symptomatic heart failure and nonischemic cardiomyopathy.

In the present report, sample size precluded a detailed analysis of gender differences because of the relatively small number of events in women.

**Study limitations.** The present cross-sectional study included 154 patients with a peak VO₂ ≤14 ml/min per kg. There were only 34 patients with a peak exercise VO₂ ≤10 ml/min per kg, limiting the ability to study predictors of mortality in the latter patient subset. Many such patients have significant dyspnea during exercise, making it difficult to measure ventilatory gas variables with a mouthpiece or face mask. In some earlier reports, bicycle ergometry was used to measure peak VO₂ rather than treadmill exercise, as was used in the present study. Peak VO₂ with treadmill exercise is usually greater than that achieved with bicycle ergometry. Therefore, our results cannot be strictly compared with studies in which bicycle ergometry was used.

We chose a cutpoint of 120 mm Hg to assess exercise SBP as a predictor of mortality. The measurement was made by sphygmomanometry, not central arterial measurements. Peak SBP measurements during exercise are also influenced by technique and sampling frequency. Vasodilator drug therapy may also limit exercise SBP response. In the present retrospective report, we were not able to measure all antihypertensive drug therapy at the time of exercise testing. Exercise capacity can be significantly improved by participation in a cardiac rehabilitation program. We did not monitor compliance or physical activity, such as walking and cycling, or other leisure time and occupational activity in follow-up and thus cannot assess the impact of sedentary versus exercise activities on exercise test performance.

**Conclusions.** Our findings confirm and extend previous observations that cardiopulmonary exercise testing is useful in estimating prognostic risk in patients with CHF and refine the cardiopulmonary test indications for heart transplantation. In particular, in patients with a peak exercise VO₂ ≤14 ml/min per kg, the inability to increase exercise SBP to >120 mm Hg is a powerful predictor of subsequent mortality, and percent predicted peak VO₂ ≤50% is an important predictor of cardiac events, particularly subsequent cardiac deterioration leading to hospital admission and listing as Status 1 transplant priority.
References


