Peak Oxygen Uptake Better Predicts Outcome Than Submaximal Respiratory Data in Heart Transplant Candidates

Karel Pardaens, PhD; Johan Van Cleemput, MD; Johan Vanhaecke, MD, PhD; Robert H. Fagard, MD, PhD

Background—Many studies have focused on the prognostic power of peak oxygen uptake (V\textsuperscript{\textcircled{O}}\textsubscript{2}) in patients with chronic heart failure, but maximal exercise testing is not without risk. The purpose of the present study was, therefore, to assess the prognostic significance of the steepness of changes in ventilation and carbon dioxide output (V\textsuperscript{\textcircled{CO}}\textsubscript{2}) during submaximal exercise in comparison with V\textsuperscript{\textcircled{O}}\textsubscript{2}.

Methods and Results—The study population consisted of 284 adult heart transplant candidates who performed a graded maximal bicycle ergometer test with respiratory gas analysis. Using the respiratory data up to a gas exchange ratio of 1.0, 3 submaximal slopes were calculated in each patient. During follow-up (median, 1.33 years), 57 patients died and 149 had \textsuperscript{1} cardiovascular event. When using Cox proportional hazards analysis, both peak V\textsuperscript{\textcircled{O}}\textsubscript{2} and submaximal respiratory slopes predicted outcome before and after accounting for age, sex, and body mass index. However, whereas the prognostic power of peak V\textsuperscript{\textcircled{O}}\textsubscript{2} was independent of submaximal respiratory data, the prognostic significance of the slopes was lost after controlling for peak V\textsuperscript{\textcircled{O}}\textsubscript{2}. Stepwise regression analysis even selected peak V\textsuperscript{\textcircled{O}}\textsubscript{2} as an independent prognostic index among the following factors: cause of heart failure, ejection fraction, pulmonary vascular resistance, natremia, and the forced expiratory volume in 1 s.

Conclusions—Respiratory data during submaximal exercise are significant predictors of outcome in patients with chronic heart failure, but their prognostic power is inferior to that of peak V\textsuperscript{\textcircled{O}}\textsubscript{2}. However, these data may be useful when maximal exercise is contraindicated or not achievable. (Circulation. 2000;101:1152-1157.)

Key Words: exercise ■ heart failure ■ prognosis ■ transplantation

Impaired exercise tolerance is predictive of mortality in patients with advanced chronic heart failure (CHF).\textsuperscript{1-13} Therefore, current guidelines recommend using maximal exercise testing to select appropriate candidates for heart transplantation (HTx).\textsuperscript{14} Peak oxygen uptake (V\textsuperscript{\textcircled{O}}\textsubscript{2}), obtained during maximal exercise testing, has been the gold standard of exercise performance. However, because maximal exertion is not without risk in patients with CHF and is, in fact, not reached by a number of patients, it is worthwhile to examine whether submaximal data, such as the ventilatory responses to exercise, might provide prognostic information similar to peak V\textsuperscript{\textcircled{O}}\textsubscript{2}.

Chua and colleagues\textsuperscript{1} showed that a steeper slope of minute ventilation (VE) on carbon dioxide output (V\textsuperscript{\textcircled{CO}}\textsubscript{2}) carries a worse prognosis for patients, over and above peak V\textsuperscript{\textcircled{O}}\textsubscript{2}, but they calculated the VE-V\textsuperscript{\textcircled{CO}}\textsubscript{2} slope up to maximal exercise. It is, therefore, uncertain whether the VE-V\textsuperscript{\textcircled{CO}}\textsubscript{2} slope would predict outcome when calculated up to a submaximal exercise level. To the best of our knowledge, only one recent study examined the prognosis in CHF patients from submaximal exercise data. De Vries et al\textsuperscript{6} constructed a formula to predict maximal exercise capacity on the basis of several parameters measured during the first 6 minutes of a maximal exercise test. The authors demonstrated that predicted peak V\textsuperscript{\textcircled{O}}\textsubscript{2} was related to outcome, independent of general characteristics but not of data obtained at peak exercise. In other words, submaximal data provided less prognostic information than maximal exercise data. However, the VE-V\textsuperscript{\textcircled{CO}}\textsubscript{2} slope was not computed in the latter study, so it remains uncertain whether such respiratory slopes up to a submaximal exercise level would be better predictors of outcome than maximal measurements.

The purpose of the present study was to assess the prognostic significance of 3 slopes derived from relationships between respiratory variables during submaximal exercise using data up to a respiratory gas exchange ratio (RQ) of 1.0.
An attempt was made to answer the following 3 research questions. (1) Do both peak \( V\bar{O}_2 \) and submaximal data (the slopes up to an \( RQ \) of 1.0) predict outcome? (2) Is the prognostic power of peak \( V\bar{O}_2 \) superior to that of submaximal data? (3) What is the value of the exercise parameters when compared with nonexercise data?

**Methods**

**Patient Selection**
Between May 1991 and December 1996, 671 patients were referred to our center for assessment of their suitability for HTx. Of this cohort, we followed the 289 patients (43%) who performed an exercise test during the pre-HTx work-up. All patients were adult (aged 18 to 69 years), white individuals except 2; these 2 patients were excluded from the analyses (one was 15 years old and one was black). Two patients were not eligible because of a severe locomotor disorder. A last patient was excluded because of a fatal ventricular fibrillation in the recovery phase of the exercise test. Thus, 284 patients were considered in the present report.

**Baseline Data: The pre-HTx Work-Up**
All patients performed a maximal bicycle ergometer test after having provided oral informed consent. The test always took place before noon, without interruption of medical treatment. After \( \geq 2 \) minutes of sitting rest on the bicycle, patients started cycling at a workload of 10 W, which was increased by 10 W after each minute. Patients were encouraged to exercise until they felt unable to continue. At rest and during exercise, \( V\bar{O}_2, V\bar{CO}_2 / L/min \), and VE (L/min) were measured continuously using a mixing chamber (Sensormedics 2900). Peak \( V\bar{O}_2 \) was defined as the highest \( V\bar{O}_2 \) during any stage that could be sustained for 1 minute; in most instances, this corresponded to the highest workload that was sustained for 1 minute (ie, peak workload). Peak \( V\bar{O}_2 \) is reported in absolute units (L/min), after correction for body weight \( (mL \cdot min^{-1} \cdot kg^{-1}) \), and as a percentage of predicted normal values accounting for age, weight, and sex.\(^{15}\)

Peak \( RQ \) (ie, \( V\bar{CO}_2/V\bar{O}_2 \)) was defined as the highest \( 20+ \)-value at the end of exercise. In each individual patient, respiratory data from rest to an \( RQ \) of 1.0 were used to calculate the slope (ie, the regression coefficient) between the square root of \( V\bar{CO}_2 \) and the square root of \( V\bar{O}_2 \).\(^{16,17}\) The slope of the logarithmically transformed VE on \( V\bar{O}_2 \) and the slope of VE on \( V\bar{CO}_2 \) have shown a linear relationship between these pairs of variables. In patients who did not achieve a peak \( RQ \) of 1.0 (\( n=61; 22\% \)), the slopes were calculated using all data from rest to the end of exercise. Slopes could not be determined in 11 patients because of technical problems during exercise testing. Heart rate was derived from the ECG at the end of the sitting rest period and throughout the exercise test.

Nonexercise parameters were considered to assess whether exercise-derived variables would have independent prognostic value. To prevent "overfitting" by considering too many predictor variables in the regression models,\(^{22} \) we decided to use the following 4 biologically unrelated variables, which have a proven relationship with severity of CHF:\(^{5,9,10,13,23-25} \); radionuclide left ventricular ejection fraction (%; determined in 259 patients), pulmonary vascular resistance (mm Hg \( \cdot L^{-1} \cdot min^{-1} \); \( n=268 \)), serum sodium concentration (mmol/L; \( n=283 \)), and the forced expiratory volume in 1 s (FEV1; \( n=274 \); expressed in absolute values [liters] and as a percentage of predicted normal values according to age, height, and sex).\(^{26} \) All data were available in 243 patients.

**Outcome Data: Follow-Up**
Data collection on follow-up was started in January 1997 and finished by the end of the year. The aim was to obtain information on the patients’ vital and health status starting at the date of the exercise test. In the first phase, local hospital files were checked. If patients had not been followed in our hospital until 1997 or if data were considered incomplete, a questionnaire concerning vital and health status was sent to the patient’s physician(s). If deemed necessary, doctors and—exceptionally—patients were contacted by telephone. Objective evidence was required for acceptance of an event, and 2 investigators (K.P. and R.F.) had to agree on the interpretation of the available information.

**Statistical Analyses**
The SAS software (SAS Institute) was used for all statistical analyses. Variables were coded as 1 when the condition was present and 0 when absent. Single regression analysis was used to calculate slopes (ie, regression coefficients). Characteristics of survivors and nonsurvivors and of patients who had versus those who did not have events were compared using unpaired Student’s \( t \)-tests and \( \chi^2 \) analysis. The Cox proportional hazards regression model was used for survival analysis.\(^{27} \) We examined whether the data obtained during the pre-HTx work-up were predictive for either the time to death (all-cause mortality) or the time to the first-occurring fatal or nonfatal cardiovascular event. Patients who underwent transplantation were censored at the time of HTx in all analyses. The prognostic value of a parameter is given by its relative hazard rate, which estimates how much the incidence of an event changes when the independent variable increases by 1 unit. \( P<0.05 \) was considered significant.

**Results**

**Patient Characteristics at Baseline and Follow-Up Data**
Tables 1 and 2 present the characteristics of the patient population at baseline, including data obtained during exercise testing. Exercise was limited by general fatigue, leg fatigue, or dyspnea in most patients (\( n=245; \ 86\% \)); other tests were terminated because of ST depression, angina pectoris, or an arrhythmia (\( n=18; \ 6\% \)) or for other reasons, such as anxiety (\( n=21; \ 7\% \)). Table 3 summarizes the corre-
TABLE 2. Data Collected During the Exercise Test

<table>
<thead>
<tr>
<th>Data at rest sitting, before exercise</th>
<th>Data collected during the course of exercise: slopes up to an RQ=1.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinus rhythm</td>
<td>√VCO₂-VO₂, ×10²</td>
</tr>
<tr>
<td></td>
<td>logVE-VO₂, ×10³</td>
</tr>
<tr>
<td></td>
<td>VE-VO₂, ×10⁻¹</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>2.2±0.4</td>
</tr>
<tr>
<td></td>
<td>1.8±0.7</td>
</tr>
<tr>
<td></td>
<td>3.8±1.1</td>
</tr>
<tr>
<td></td>
<td>84±16</td>
</tr>
<tr>
<td>Data at peak exercise</td>
<td></td>
</tr>
<tr>
<td>Peak VO₂, L/min</td>
<td>1.07±0.42</td>
</tr>
<tr>
<td></td>
<td>14.9±5.0</td>
</tr>
<tr>
<td></td>
<td>46±14</td>
</tr>
<tr>
<td></td>
<td>82±34</td>
</tr>
<tr>
<td>Peak work load, W</td>
<td>134±27</td>
</tr>
<tr>
<td>Peak heart rate, beats/min</td>
<td>1.09±0.14</td>
</tr>
<tr>
<td>Peak RO</td>
<td>8.3±3.1</td>
</tr>
</tbody>
</table>

Values are mean±SD or No. of patients (%).

TABLE 3. Analysis of Submaximal Respiratory Data: Slopes up to RQ=1.0

<table>
<thead>
<tr>
<th>Correlation Coefficients*</th>
<th>Correlation Coefficients With Peak VO₂, L/min†</th>
<th>Correlation Coefficients With Peak VO₂, mL · min⁻¹ · kg⁻¹‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>√VCO₂-VO₂ slope</td>
<td>0.996 (0.895–0.999)</td>
<td>−0.68‡</td>
</tr>
<tr>
<td>logVE-VO₂ slope</td>
<td>0.988 (0.678–0.999)</td>
<td>−0.71‡</td>
</tr>
<tr>
<td>VE-VCO₂ slope</td>
<td>0.997 (0.884–0.999)</td>
<td>−0.50‡</td>
</tr>
</tbody>
</table>

*Values are expressed as median (range) of the correlation coefficient in each patient, reflecting the relationship between the 2 variables of each slope.
†Almost identical results were obtained when the analysis was limited to the 237 subjects who stopped the exercise test for either general fatigue, leg fatigue, or dyspnea.
‡P<0.001.

TABLE 4. Data on Follow-Up

<table>
<thead>
<tr>
<th>First-Occurring Fatal or Nonfatal Cardiovascular Event</th>
<th>All-Cause Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalization for heart failure</td>
<td>84</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>2</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>5</td>
</tr>
<tr>
<td>Cardiac surgery</td>
<td>19</td>
</tr>
<tr>
<td>Peripheral arterial accidents</td>
<td>3</td>
</tr>
<tr>
<td>Symptomatic malignant arrhythmias*</td>
<td>12</td>
</tr>
<tr>
<td>Unexplained sudden death†</td>
<td>21</td>
</tr>
<tr>
<td>Death from heart failure</td>
<td>3</td>
</tr>
<tr>
<td>Noncardiovascular death†</td>
<td>NA</td>
</tr>
<tr>
<td>Total</td>
<td>149</td>
</tr>
</tbody>
</table>

Values are numbers of patients.
*Symptomatic malignant arrhythmias included ventricular tachycardia (with or without syncope) necessitating hospitalization and documented ventricular fibrillation or cardiac arrests.
†Unexplained sudden death included instantaneous death, death within 24 hours after the onset of symptoms, found dead, or unexpected death.
‡Two patients died from cancer and one died from the sequelae of a bronchopulmonary infection.

Prognostic Value of Patient Characteristics

Nonsurvivors were older (P<0.05) and had a higher prevalence of ischemic heart disease (P<0.01) and a lower FEV1 (in absolute and in normalized values; P<0.01) than survivors; the other characteristics were similar in both groups. Characteristics did not differ between patients who did and did not experience cardiovascular events, except for normalized FEV1, which was significantly lower (P<0.05) in patients who had an event. Single Cox regression analysis identified age as a significant predictor of all-cause mortality (P=0.01) but not of the first-occurring fatal or nonfatal cardiovascular event. The same was true for ischemic heart disease, but a diagnosis of idiopathic cardiomyopathy was associated with better (P<0.01) survival and a lower incidence of all cardiovascular events (P<0.05). A higher pulmonary vascular resistance (P<0.05), a lower serum sodium concentration (P<0.05), and a lower FEV1 (P<0.05) consistently carried a worse prognosis (ie, both time to death and
time to the first-occurring cardiovascular event were significantly lower). The other characteristics, including medication and left ventricular ejection fraction, did not have prognostic significance.

### Prognostic Value of Exercise Data

Nonsurvivors had a steeper \( \sqrt{V\dot{C}_{O2}-V\dot{O}_2} \) slope \((P<0.05)\) and a lower exercise tolerance (peak \( V\dot{O}_2 \) [L/min], \( P<0.05 \); peak \( V\dot{O}_2 \) [mL · min\(^{-1} \) · kg\(^{-1} \)], \( P<0.001 \); peak \( V\dot{O}_2 \) [% predicted], \( P<0.05 \); peak workload, \( P<0.01 \)) than survivors; the other data collected during exercise testing (including the \( V\dot{E}\)-\( V\dot{C}_{O2} \) slope and \( \log V\dot{E}\)-\( V\dot{C}_{O2} \) slope) were similar among the 2 groups. None of the parameters differed between the patients who had versus those who did not have cardiovascular events. In single Cox regression analysis, data measured at rest before exercise (Table 5) were not related to outcome, except that the presence of sinus rhythm predicted a lower incidence of cardiovascular events \((P<0.05)\). Of the data obtained during exercise, steeper slopes, a lower peak \( V\dot{O}_2 \), a lower peak heart rate univariately predicted higher mortality.

Peak heart rate did not predict mortality independently of peak \( V\dot{O}_2 \). The relative hazard rate of 0.89 for weight-adjusted peak \( V\dot{O}_2 \) indicates that a 1 mL · min\(^{-1} \) · kg\(^{-1} \) higher peak \( V\dot{O}_2 \) is associated with an 11% lower mortality throughout the observation period. The results obtained by using single regression analysis remained similar (eg, peak \( V\dot{O}_2 \)) or became somewhat weaker (eg, submaximal slopes) after adjustment for age, sex, and body mass index (Table 5). The predictive power of exercise data were, in general, lower when the first-occurring cardiovascular event was considered as the end point of interest (Table 5). Results were not substantially altered when only cardiovascular deaths \((n=54)\) instead of all-cause mortality \((n=57\) deaths) were considered.

### Comparison of the Prognostic Value of Maximal and Submaximal Exercise Data

In the next step, we compared the prognostic value of submaximal exercise data with peak \( V\dot{O}_2 \). The results are given for the \( \sqrt{V\dot{C}_{O2}-V\dot{O}_2} \) slope, which is representative of the other slopes. Figure 1A presents the prognostic value of peak \( V\dot{O}_2 \) when accounting for the submaximal \( \sqrt{V\dot{C}_{O2}-V\dot{O}_2} \) slope, whereas Figure 1B depicts the prognostic value of the \( \sqrt{V\dot{C}_{O2}-V\dot{O}_2} \) slope when accounting for the prognostic value of peak \( V\dot{O}_2 \). The prognostic significance of peak \( V\dot{O}_2 \) was independent of the slope, but that of the slope was lost by controlling for peak \( V\dot{O}_2 \). Stepwise regression models containing the 3 slopes but not peak \( V\dot{O}_2 \) showed that the prognostic value of the slopes was not additive.

### Prognostic Value of Exercise Data Compared With Nonexercise Data

A stepwise regression model with general characteristics (age, sex, body mass index, and cause of heart failure) and established, nonexercise prognostic indices (FEV1, natremia, pulmonary vascular resistance, and left ventricular ejection fraction) selected peak \( V\dot{O}_2 \) as an independent predictor of mortality \((P<0.01)\), together with sex \((P<0.05)\) as the only significant covariate. Pulmonary vascular resistance \((P<0.001)\) and natremia \((P<0.05)\) were identified as the only predictors of the first cardiovascular event. Figure 2 shows the risk for mortality and the incidence of cardiovascular events after 2 years of follow-up.
The prog nostic value of peak \( \dot{V}O_2 \) was comparable after accounting for the reason for terminating the exercise test; stopping the exercise test for a noncardiac reason was in itself not related to outcome.

**Discussion**

To select the most suitable HTx candidates, one must rely on pretransplant investigations with proven prognostic value. We focused on some established and some novel parameters obtained during exercise testing.

**The Prognostic Value of Peak \( \dot{V}O_2 \)**

In a relatively large number of patients and with an accurate follow-up of a reasonable duration, the present study comes to similar conclusions as previous reports regarding the predictive power of peak \( \dot{V}O_2 \) for transplant-free survival in patients with CHF and the fact that the prognostic value of peak \( \dot{V}O_2 \) is independent of anthropometric and demographic characteristics. Similar results were obtained when the first-occurring cardiovascular event instead of death was the end point of interest. Moreover, the predictive power of peak \( \dot{V}O_2 \) was maintained when accounting for submaximal respiratory data, but not vice versa. However, when maximal exercise is contraindicated or not achievable, the submaximal slopes provide reasonable alternatives. The analyses indicate that the slopes have significant prognostic power, but that this power is less than peak \( \dot{V}O_2 \). Peak \( \dot{V}O_2 \) even predicts outcome independently of nonexercise parameters. In addition, the prognostic value of peak \( \dot{V}O_2 \) might have been underestimated because it was at least partly taken into account in the decision regarding HTx, and patients were censored at the time of HTx.

**The Prognostic Value of Submaximal Exercise Data**

The VE-V\( \dot{CO}_2 \) slope has frequently been considered in the heart failure literature in the past few years. Chua et al demonstrated that the VE-V\( \dot{CO}_2 \) slope gave additional prognostic information beyond peak \( \dot{V}O_2 \) in patients with heart failure, but they determined the slope using data up to maximal exercise. Because the VE-V\( \dot{CO}_2 \) relationship is linear, we reasoned that it should be possible to calculate the slopes using the data up to a predefined submaximal exercise level, such as an RQ of 1.0, and, hence, investigate the prognostic value of these slopes. Likewise, we considered the \( \sqrt{VCO_2-VO_2} \) slope and the logVE-V\( \dot{O}_2 \) slope, which have been described previously and were found to be linear. These latter slopes relate to anaerobic energy delivery during exercise, and the logVE-V\( \dot{O}_2 \) slope also reflects ventilatory efficiency, just like the VE-V\( \dot{CO}_2 \) slope. All slopes predicted outcome, but the prognostic value was lost after adjustment for peak \( \dot{V}O_2 \). Similarly, de Vries et al recently investigated whether peak \( \dot{V}O_2 \), estimated from the initial stages of exercise testing, would predict mortality. The authors essentially came to the same conclusion: data from the initial stages of testing provided independent prognostic information only when making abstractions of the data obtained at peak exercise.

It should be acknowledged that many of the alleged submaximal tests (eg, the 6-minute walk test) are, in fact,
supramaximal tests. Some patients with CHF are not able to walk for 6 minutes, and in this study, 21% of the patients did not achieve an RQ of 1.0. We also did not analyze more than half of the total cohort of patients referred between 1991 and 1996 for a pre-HTx evaluation: the patients who did not perform an exercise test were not considered. Although patients with a cardiac contraindication to exercise testing are reported to have a very poor prognosis,11 we think that we excluded patients at both ends of the heart failure spectrum because patients were not asked to exercise if their clinical status was either critical or too good. Thus, we considered a group of patients in whom prognostic precision is required to select the most suitable candidates for HTx.

Conclusions

Respiratory data during submaximal exercise are significant predictors of outcome in patients with CHF, but their prognostic power is inferior to that of peak VO2. However, these data may be useful when maximal exercise is contraindicated or not achievable.

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References

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