Exercise Anaerobic Threshold and Ventilatory Efficiency Identify Heart Failure Patients for High Risk of Early Death

Anselm K. Gitt, MD; Karlman Wasserman, MD, PhD; Caroline Kilkowski, MD; Thomas Kleemann, MD; Andreas Kilkowski, MD; Matthias Bangert, MD; Steffen Schneider, PhD; Armin Schwarz, MD; Jochen Senges, MD, FESC

Background—The maximal oxygen uptake (peak VO₂) is used in risk stratification of patients with chronic heart failure (CHF). Peak VO₂ might be lower than maximally possible if exercise is stopped early because of lack of patient motivation or premature cessation by the investigator. In contrast, the anaerobic threshold (VO₂AT) and the ventilatory efficiency (VE versus VCO₂ slope) are less subject to these influences. Thus, we compared these parameters with peak VO₂ in identifying patients with CHF at increased risk for death within 6 months after evaluation.

Methods and Results—We performed cardiopulmonary exercise tests with gas exchange measurements in 223 consecutive patients with CHF (114 coronary artery disease, 92 dilated cardiomyopathy, 17 others) at the Herzzentrum Ludwigshafen between 1995 and 1998. We measured peak VO₂, VO₂AT and VE versus VCO₂ slope. We selected peak VO₂ of ≤14 mL/kg per minute, VO₂AT of <11 mL/kg per minute, and VE versus VCO₂ slope of >34 as threshold values for high risk of death. The median follow-up time was 644 days. Patients with peak VO₂ of ≤14 mL/kg per minute had a 3-fold increased risk (OR=3.4; CI, 1.3 to 9.1), with VO₂AT <11 mL/min per kg or VE versus VCO₂ slope >34 a 5-fold increased risk for early death (OR=5.3; CI, 1.5 to 19.0; OR=4.8; CI, 1.7 to 13.8, respectively). In patients with both VO₂AT <11 mL/kg per minute and VE versus VCO₂ slope >34, the risk of early death was 10-fold higher (OR=9.6; CI, 2.1 to 44.7). After correction for age, sex, left ventricular ejection fraction, and New York Heart Association class in a multivariate analysis, the combination of VO₂AT <11 mL/kg per minute and VE versus VCO₂ slope >34 was the best predictor of 6-month mortality (RR=5.1, P=0.001).

Conclusions—VO₂AT of <11 mL/kg per minute and slope of VE versus VCO₂ >34, combined, better identified patients at high risk for early death from CHF than did peak VO₂ and should therefore be considered when prioritizing patients for heart transplantation. (Circulation. 2002;106:3079-3084.)

Key Words: heart failure ■ exercise ■ transplantation ■ ventilation ■ prognosis

Despite recent advances in pharmacological treatment of patients with chronic heart failure (CHF), including ACE inhibitors and β-blockers,1-4 mortality rates in patients with severe CHF remain high. Reliable risk stratification is a continuing challenge as the number of candidates for heart transplantation is increasing and the supply of donor hearts is limited. Because of the supply-demand mismatch, many patients die while they are on the waiting list for transplantation. The identification of patients at highest risk for early death from heart failure, therefore, is of special importance.

Besides classic risk factors such as left ventricular ejection fraction (LVEF), New York Heart Association class IV symptoms, and neurohormonal markers, peak VO₂ was found to predict survival in patients with CHF.5-8 Mancini et al9 reported that patients with heart failure with a peak VO₂ >14 mL/kg per minute had a 1-year survival rate similar to that of patients receiving heart transplantation. Increasing experience has confirmed the prognostic value of peak VO₂ in the evaluation for heart transplantation.10-15 The 24th Bethesda Conference for Cardiac Transplantation16 listed peak VO₂ <10 mL/kg per minute with achievement of anaerobic metabolism as an accepted indication for heart transplantation. Patients with a peak VO₂ ≤14 mL/kg per minute and major limitation of daily activities were also transplantation candidates.

Peak VO₂ might be underestimated because of reduced patient motivation as well as premature termination of exercise by the examiner. The anaerobic threshold (VO₂AT) measures the sustainable O₂ uptake and is an objective parameter of cardiopulmonary exercise capacity that can be derived from submaximal exercise testing and therefore is independent of the influences described above.17 However, data showing its prognostic value in CHF do not yet exist.

Recently, ventilatory efficiency, measured as the slope of VE versus VCO₂ below the ventilatory compensation point for...
exercise metabolic acidosis, was found to be a reliable predictor of prognosis in patients with CHF.\textsuperscript{18,19} As with VO\textsubscript{2}AT, it can be derived from submaximal exercise testing and is independent of patient motivation.

In this study, we sought to determine the predictive value of VO\textsubscript{2}AT, of VE versus V\textsubscript{CO\textsubscript{2}} slope, and the combination of both for estimating the short-term (6-month) and long-term (2-year) survival of patients with CHF and to compare these parameters with survival predicted by peak VO\textsubscript{2}/kg.

### Methods

#### Patients

The study included 223 consecutive patients with CHF referred to the Herzzentrum Ludwigshafen who performed progressively increasing, symptom-limited cardiopulmonary exercise testing with gas exchange measurements between February 1995 and October 1998. All patients were referred by physicians in the catchment area of the Herzzentrum Ludwigshafen, had heart failure for at least 3 months, and were receiving stable doses of their medications without exacerbation of symptoms or need for intravenous inotropic support during 4 weeks preceding exercise testing. Patients with severe concomitant extracardiac diseases limiting exercise performance were excluded. Informed consent was obtained from each patient. The baseline demographic and clinical characteristics are shown in Table 1.

#### Cardiopulmonary Exercise Testing

All patients performed upright bicycle exercise to maximum tolerance with the use of a progressively increasing work rate at 10 to 20 W/min after a period of resting and unloaded pedaling, as recommended by Buchfuhrer et al.\textsuperscript{20} Patients were encouraged to exercise until symptoms were intolerable. Investigator-determined exercise end points were severe ventricular tachycardia of $>5$ beats, high degree of AV block, ST-segment depression $>3$ mm, systolic blood pressure $>250$ mm Hg, or progressive decrease in blood pressure.

Breath-by-breath gas exchange measurements were performed with a MedGraphics CardiO2 metabolic cart. Oxygen uptake (VO\textsubscript{2}), carbon dioxide output (V\textsubscript{CO\textsubscript{2}}), tidal volume (V\textsubscript{T}), and breathing rate were measured. Blood gases (Pa\textsubscript{O\textsubscript{2}}, Pa\textsubscript{CO\textsubscript{2}}) and pH were measured at rest and shortly before the end of exercise with the use of arterialized capillary blood samples from the hyperemic earlobe.

#### Cardiopulmonary Parameters

From the above data, minute ventilation (VE), respiratory exchange ratio (V\textsubscript{CO\textsubscript{2}}/VO\textsubscript{2}), the O\textsubscript{2}-pulse (VO\textsubscript{2}/HR), and the ventilatory equivalents for O\textsubscript{2} and CO\textsubscript{2} (Ve\textsubscript{O\textsubscript{2}}/Ve\textsubscript{CO\textsubscript{2}}) were calculated. Peak VO\textsubscript{2} was determined as the highest VO\textsubscript{2} achieved during exercise.

The anaerobic threshold (VO\textsubscript{2}AT) was measured by the V-slope method.\textsuperscript{21} Typical changes in ventilatory equivalents and end-tidal gas concentrations (PET\textsubscript{O\textsubscript{2}} and PET\textsubscript{CO\textsubscript{2}}) were examined to search for agreement in cases that were questionable with regard to the precise VO\textsubscript{2}AT value. Predicted peak VO\textsubscript{2} was determined by using the regression equations of Wasserman et al.\textsuperscript{13} The VE versus V\textsubscript{CO\textsubscript{2}} slope was calculated by linear regression, excluding the nonlinear part of the data after the onset of ventilatory compensation for metabolic acidosis. Referring to published data on prognosis in patients with CHF, we selected peak VO\textsubscript{2} of $\leq 14$ mL/kg per minute or $\leq 50$% normal,\textsuperscript{14} VO\textsubscript{2}AT $< 11$ mL/kg per minute,\textsuperscript{22-24} and a VE versus V\textsubscript{CO\textsubscript{2}} slope $> 34$\textsuperscript{14} as threshold values to identify patients with CHF with an increased risk of death.

#### Follow-Up Data on Prognosis

All patients were followed at the Herzzentrum Ludwigshafen. The outcome data were prospectively collected by telephone interviews of the patient or the patient’s family or by information from the residents’ registration office. The median follow-up period was 644 days.

#### Statistical Analysis

Continuous variables are expressed as mean$\pm$1 SD. Discrete variables are shown as absolute values and/or percentages $\pm$ SD. Simple linear regression analysis was used to examine VE versus V\textsubscript{CO\textsubscript{2}} slope as a function of peak VO\textsubscript{2} and VO\textsubscript{2}AT. $\chi^2$ testing was used for analysis of categoric variables. The log rank test was used to compare differences among subgroups of the patients with CHF. Diagnostic test analysis was performed to calculate sensitivity, specificity, and positive predictive and negative predictive values for the different threshold values. The prognostic values of VE versus V\textsubscript{CO\textsubscript{2}} slope, peak VO\textsubscript{2}, VO\textsubscript{2}AT, LVEF, and NYHA class were assessed by using a multiple Cox regression analysis. Survival curves were constructed by using the Kaplan-Meier product limit method and were compared with the log rank test. We used a likelihood ratio test according to Wald in the logistic regression model to test for differences between odds ratios. A value of $P<0.05$ was considered significant. All calculations were performed with the use of the SAS statistical package, version 6.12 (SAS Institute, Inc.).

### Results

#### Baseline Characteristics

Descriptive characteristics of the study population are presented in Table 1. Ischemic cardiomyopathy was the predominant underlying cause of CHF (114 patients, 51%). LVEF was reduced to 28.7$\pm$8.1%; the left ventricular end-diastolic diameter was 65$\pm$7 mm. All patients had symptomatic heart failure, with mean NYHA class of 2.1$\pm$0.7. The medical
The mean vital capacity (VC) of all patients was 88% of normal. The nonsurvivors showed a more restrictive pattern expressed by a lower VC than survivors. The nonsurvivors had a slightly lower average PaCO\textsubscript{2} at rest and at peak exercise compared with survivors. Dead space fractions of VE/(V\textsubscript{E}R) were increased to 0.62 and 0.49, during rest and peak exercise, respectively (Table 2).

### Follow-Up on Survival

None of the patients were lost to follow-up. During the median follow-up of 644 days, 46 patients died (nonsurvivors). Four patients with an ICD had ventricular fibrillation, detected and successfully treated by the ICD. Twenty patients died within the first 6 months of follow-up. None of the patients were lost to follow-up. During the median follow-up of 644 days, 46 patients died (nonsurvivors). Eight patients because of their lower maximal work rate.

### Cardiopulmonary Exercise Testing

Exercise was stopped for dyspnea in 141 patients, angina in 22 patients, and fatigue or exhaustion in 40 patients. The remaining 20 patients were stopped for investigator-determined end points described in the Methods section. The anaerobic threshold could not be determined in 17 patients (8%) because of mitigating oscillatory gas exchange patterns or premature end of exercise. All measurements of exercise capacity were lower in nonsurvivors than survivors (Table 2). There was no difference in heart rate at rest or at maximal exercise between both groups. The O\textsubscript{2}-pulse was lower in nonsurvivors than in survivors. VE at maximal exercise was lower in nonsurvivors because of their lower maximal work rate.

### Cardiopulmonary Predictors of Long-Term Mortality

Peak V\textsubscript{O\textsubscript{2}} \leq 14 , peak V\textsubscript{O\textsubscript{2}} \leq 50% normal, VE versus VCO\textsubscript{2} slope >34, and V\textsubscript{O\textsubscript{2}}AT <11 were significant predictors of death in CHF during the median follow-up of 644 days (Figure 1). Peak V\textsubscript{O\textsubscript{2}} \leq 14 and V\textsubscript{O\textsubscript{2}}AT <11 were more predictive, with odds ratios of 3.9 and 3.7 than the percent of predicted peak V\textsubscript{O\textsubscript{2}} and the VE versus VCO\textsubscript{2} slope with odds ratios of 2.5 and 3.0, respectively. V\textsubscript{O\textsubscript{2}}AT <11 identified 4 additional nonsurvivors not identified by peak V\textsubscript{O\textsubscript{2}} \leq 14 (Figure 2). In patients with peak V\textsubscript{O\textsubscript{2}} \leq 14 and VE versus VCO\textsubscript{2} slope >34, the increased risk of death was 6.1 times (Figure 1); whereas the combination of VE versus VCO\textsubscript{2} slope >34 and V\textsubscript{O\textsubscript{2}}AT <11 increased risk of death 7.0 times during follow-up (P<0.001, Figure 1). Thirty-six of 46 nonsurvivors

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**Table 2: Lung Function, Blood Gases, Exercise Characteristics of the Study Population (n=223), and Differences Between Survivors and Nonsurvivors**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients (n=223)</th>
<th>Survivors (n=177)</th>
<th>Nonsurvivors (n=46)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lung function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VC, % normal</td>
<td>88±17</td>
<td>91±16</td>
<td>77±19</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FEV\textsubscript{1}, L/s</td>
<td>2.78±0.88</td>
<td>2.91±0.86</td>
<td>2.30±0.78</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FEV\textsubscript{1}/VC, %</td>
<td>78±11</td>
<td>78±11</td>
<td>78±12</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Blood gases</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pac\textsubscript{o2} peak exercise, mm Hg</td>
<td>79.8±12.4</td>
<td>80.0±12.6</td>
<td>78.9±12.0</td>
<td>NS</td>
</tr>
<tr>
<td>Pac\textsubscript{o2} rest, mm Hg</td>
<td>40.4±4.9</td>
<td>40.8±4.5</td>
<td>39.0±6.0</td>
<td>0.007</td>
</tr>
<tr>
<td>Pac\textsubscript{o2} peak exercise, mm Hg</td>
<td>38.0±5.3</td>
<td>38.7±5.1</td>
<td>35.2±5.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Exercise data</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate at rest, bpm</td>
<td>82±15</td>
<td>82±16</td>
<td>84±13</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate at peak exercise, bpm</td>
<td>118±24</td>
<td>119±24</td>
<td>112±22</td>
<td>NS</td>
</tr>
<tr>
<td>Maximal work load, W</td>
<td>96±53</td>
<td>102±52</td>
<td>72±46</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PeakVO\textsubscript{2}, mL/kg per minute</td>
<td>15.8±5.3</td>
<td>16.4±5.3</td>
<td>13.2±4.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PeakVO\textsubscript{2}, % predicted</td>
<td>63±20</td>
<td>65±21</td>
<td>57±17</td>
<td>0.025</td>
</tr>
<tr>
<td>VO\textsubscript{2}AT, mL/kg per minute</td>
<td>11.3±3.5</td>
<td>11.6±3.6</td>
<td>10.2±3.0</td>
<td>0.008</td>
</tr>
<tr>
<td>Peak O\textsubscript{2}-pulse, mL/min per beat</td>
<td>10.5±3.2</td>
<td>10.9±3.3</td>
<td>9.3±2.3</td>
<td>0.005</td>
</tr>
<tr>
<td>V\textsubscript{E} peak exercise, L/min</td>
<td>48.5±15.3</td>
<td>50.0±15.8</td>
<td>43.0±11.9</td>
<td>0.006</td>
</tr>
<tr>
<td>V\textsubscript{E} vs V\textsubscript{CO2} slope</td>
<td>34.7±8.9</td>
<td>33.6±8.1</td>
<td>38.7±10.8</td>
<td>0.001</td>
</tr>
<tr>
<td>V\textsubscript{E} vs V\textsubscript{CO2} at rest</td>
<td>0.62±0.07</td>
<td>0.63±0.07</td>
<td>0.62±0.07</td>
<td>NS</td>
</tr>
<tr>
<td>V\textsubscript{O2}/V\text{R} peak exercise</td>
<td>0.49±0.08</td>
<td>0.49±0.08</td>
<td>0.49±0.09</td>
<td>NS</td>
</tr>
<tr>
<td>RER peak exercise</td>
<td>1.06±0.13</td>
<td>1.07±0.13</td>
<td>1.04±0.14</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Probability value for differences between survivors and nonsurvivors.
had VO$_2$AT $<$11 and 31 of 46 had a VE versus VCO$_2$ slope $>$34. Only 6 of 46 nonsurvivors had nonpathological values for either VO$_2$AT $<$11 and the VE versus VCO$_2$ slope $>$34 (Figure 3).

Survival Analysis
The Kaplan-Meier survival curves of single and combined predictors of death are shown in Figure 4. All parameters were significant predictors of death for the total follow-up of 644 days.

Cardiopulmonary Predictors of Six-Month Mortality
During the first 6 months of follow-up after the initial evaluation, peak VO$_2$ $<$50% of predicted was not predictive of early death (Figure 5). Patients with peak VO$_2$ $\leq$14 had a 3.9-fold risk, whereas patients with VE versus VCO$_2$ slope $>$34 had a 4.8-fold risk of early death. However, the best single predictor of early death was VO$_2$AT $<$11 with a 5.3-fold-increased risk (Figure 5). Combining peak VO$_2$ $\leq$14 with VE versus VCO$_2$ slope $>$34, the increased risk of death was 6.1-fold; the combination of VE versus VCO$_2$ slope $>$34 and VO$_2$AT $<$11 was 9.6-fold ($P<0.001$, Figure 5). Patients who had both VO$_2$AT $<$11 and VE versus VCO$_2$ slope $>$34 showed a 6-month mortality rate of 21.7% compared with only 2.6% in patients without these changes.

The diagnostic test analysis for the different single and combined cardiopulmonary predictors of 6-month mortality showed that the combination of VE versus VCO$_2$ slope $>$34 with VO$_2$AT $<$11 was superior to the single cardiopulmonary parameters in predicting death within 6 months, with a positive predictive value of 20.

After correcting for sex, age, LVEF, and NYHA class, all parameters were significant predictors of increased mortality rates within 6 months (Table 3). The combination of VO$_2$AT $<$11 and VE versus VCO$_2$ slope $>$34 was superior to other parameters (OR=5.1, $P=0.001$, Table 3). The chronic β-adrenergic blocker therapy was not taken into account in this multivariate analysis because it failed to predict death in univariate as well as in multivariate analysis in our patient population. The likelihood ratio test, according to Wald, in the logistic regression model to test for differences between odds ratios of different risk indicators, failed to show significance because of the large 95% CI and—for this kind of statistical test—a too-small number of patients and events in the subgroups.

Discussion
Study Findings
To our knowledge, this is the first prospective study of cardiopulmonary exercise data in consecutive patients with CHF to compare VO$_2$AT $<$11 as a predictor of early 6-month mortality with the established prognostic parameters of peak VO$_2$ $\leq$14 or peak VO$_2$ $\leq$50% predicted. By itself and in combination with VE versus VCO$_2$ slope $>$34, it identifies patients with a 2.7- and a 5.1-fold-increased risk of death within 6 months after initial evaluation, respectively, independent of sex, age, left ventricular function, and NYHA class (Table 3).

Study Population
The population of this study consisted of unselected patients with CHF treated at the Herzzentrum Ludwigshafen. Most previous studies of cardiopulmonary exercise testing in CHF were conducted in preselected patients evaluated for heart transplantation. In comparison, the patients in our study were approximately 10 years older (mean age, 63 years).
and had a higher mortality rate. The underlying cause was ischemic and nonischemic heart disease in approximately equal distribution, in contrast to a higher number of dilated cardiomyopathy in earlier studies.9,15

Most studies on the prognostic value of cardiopulmonary exercise parameters were conducted before β-adrenergic blockers were shown to be beneficial in CHF. Recent published data reported β-adrenergic blocker use in only 31% of patients with CHF.14 Forty-three percent of our study population were taking long-term β-adrenergic blocker therapy. However, the role of β-adrenergic blockade on the prognostic significance of these exercise parameters awaits a larger study with greater statistical power.

Cardiopulmonary Exercise Testing and Prognosis in Heart Failure
Peak VO₂ related to body weight has been the most widely used parameter to predict survival in patients with CHF.11,15 A value of <14 was recommended for selecting potential candidates for heart transplantation. Patients with peak VO₂ <10 had the worst prognosis. However, an actual cutoff for decision probably does not exist. Rather, there is an increasing risk of death with decreasing values of peak VO₂, as previously described.3,11 We confirmed that a peak VO₂ ≤14 signifies a worse prognosis than a higher peak VO₂ in our population of unselected patients with CHF.

A given value of peak VO₂/kg may signify a different degree of abnormality when comparing young male patients and elderly female patients. Therefore, some investigators recommended peak VO₂ expressed as percentage of the predicted maximal value, taking sex, age, and nonobese weight into account.13 Stevenson11 reported that peak VO₂/kg and the percent predicted value might be interchangeable. In our study population, peak VO₂ ≤50% normal could identify patients at increased risk for long-term but not 6-month mortality.

Chua et al18 and Kleber et al19 demonstrated the prognostic value of the ventilatory efficiency (VE versus VCO₂ slope) during exercise. We used the cutoff value of VE versus VCO₂ slope >34 to discriminate between patients at high and low risk for death. There are no data on the prognostic value of the anaerobic threshold in patients with CHF. Stevenson11 reported that VO₂ AT was essentially interchangeable with peak VO₂. Re-

Table 3. Cox Regression Analysis, Including Sex, Age, LVEF, and NYHA Class, for Calculation of Risk of Death at 6 Months

<table>
<thead>
<tr>
<th>Cardiopulmonary Parameter</th>
<th>Risk Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak VO₂ ≤14 mL/kg per minute</td>
<td>2.9</td>
<td>1.5–5.4</td>
<td>0.002</td>
</tr>
<tr>
<td>Peak VO₂ ≤10 mL/kg per minute</td>
<td>2.1</td>
<td>1.1–4.3</td>
<td>0.04</td>
</tr>
<tr>
<td>Peak VO₂ ≤50% normal</td>
<td>2.0</td>
<td>1.1–3.7</td>
<td>0.03</td>
</tr>
<tr>
<td>VO₂ AT &lt;11 mL/kg per minute</td>
<td>2.7</td>
<td>1.3–5.6</td>
<td>0.007</td>
</tr>
<tr>
<td>VE vs VCO₂ slope &gt;34</td>
<td>2.7</td>
<td>1.5–5.1</td>
<td>0.001</td>
</tr>
<tr>
<td>Peak VO₂ ≤14 + VO₂ AT &lt;11</td>
<td>3.2</td>
<td>1.5–6.7</td>
<td>0.003</td>
</tr>
<tr>
<td>Peak VO₂ ≤14 + VE vs VCO₂ slope &gt;34</td>
<td>4.5</td>
<td>2.1–10.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VO₂ AT &lt;11 + VE vs VCO₂ slope &gt;34</td>
<td>5.1</td>
<td>2.0–12.7</td>
<td>0.001</td>
</tr>
</tbody>
</table>
ferring to the Weber classification\textsuperscript{23,24} and to studies of cardiopulmonary exercise testing in preoperative evaluation of elderly patients by Older and Hall,\textsuperscript{22} we have chosen VO\textsubscript{2}AT <11 as a cutoff value for high risk. We compared the VO\textsubscript{2}AT with the peak VO\textsubscript{2} to determine their respective prognostic strengths for early (6 months) and long-term (2 years) mortality. VO\textsubscript{2}AT <11 identified additional patients to be at high risk. This parameter was as good as peak VO\textsubscript{2} in the identification of patients at increased risk for assessing long-term mortality but provided greater prognostic strength for predicting 6-month mortality. By multivariate analysis, correcting for sex, age, LVEF, and NYHA class, VO\textsubscript{2}AT <11 identified patients to have a 2.7-fold-increased risk of death at 6 months ($P=0.02$) (Table 3).

We found the same prognostic strength for the $V\dot{E}$ versus $V\dot{CO}_2$ slope as for VO\textsubscript{2}AT (Table 3). Both parameters can be derived simultaneously from the same exercise test. In contrast to peak VO\textsubscript{2}, which is strongly dependent on patient motivation to perform a maximal effort exercise, VO\textsubscript{2}AT and $V\dot{E}$ versus $V\dot{CO}_2$ slope can be determined from a submaximal effort exercise test. We therefore combined VO\textsubscript{2}AT <11 with $V\dot{E}$ versus $V\dot{CO}_2$ slope >34 for risk stratification. This combination surpassed all other parameters in their prognostic strength even after multivariate adjustment for age, sex, LVEF, and NYHA class (OR=5.1, $P<0.01$, Table 3).

**Study Limitations**

Included in this study population were only those patients who had stable CHF and who had been able to perform a symptom-limited exercise test with gas exchange measurements. Patients unable to exercise because of contraindications such as severe aortic valve disease or unstable heart failure are not represented by our study. Although we found clear differences in the relative prognostic value of the odds ratios of the various physiological measurements, there was a lack of statistical power to reach significance because of the number of patients and the number of events during the follow-up.

A further limitation is the need to study a larger number of patients who are being treated with $\beta$-adrenergic blockade to determine the prognostic value of parameters of exercise gas exchange in this population.

**Clinical Implications**

In addition to already-established prognostic values of cardiopulmonary exercise testing, our study demonstrates the high prognostic strength of VO\textsubscript{2}AT for early and long-term mortality in CHF. The combination of VO\textsubscript{2}AT <11 and the $V\dot{E}$ versus $V\dot{CO}_2$ slope >34 better identifies patients at risk for early death from CHF than peak VO\textsubscript{2} who therefore should be considered as candidates for early heart transplantation.

**References**


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