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 $\dot{V}O_2$) is used in risk stratification of patients with chronic heart failure (CHF). Peak $\dot{V}O_2$ 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 ($\dot{V}O_2\text{AT}$) and the ventilatory efficiency ($\dot{V}E$ versus $\dot{V}CO_2$ slope) are less subject to these influences. Thus, we compared these parameters with peak $\dot{V}O_2$ 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 $\dot{V}O_2$, $\dot{V}O_2\text{AT}$ and $\dot{V}E$ versus $\dot{V}CO_2$ slope. We selected peak $\dot{V}O_2$ of ≤14 mL/kg per minute, $\dot{V}O_2\text{AT}$ of <11 mL/kg per minute, and $\dot{V}E$ versus $\dot{V}CO_2$ slope of >34 as threshold values for high risk of death. The median follow-up time was 644 days. Patients with peak $\dot{V}O_2$ of ≤14 mL/kg per minute had a >3-fold-increased risk (OR=3.4; CI, 1.3 to 9.1), with $\dot{V}O_2\text{AT}$ <11 mL/min per kg or $\dot{V}E$ versus $\dot{V}CO_2$ 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 $\dot{V}O_2\text{AT}$ <11 mL/kg per minute and $\dot{V}E$ versus $\dot{V}CO_2$ 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 $\dot{V}O_2\text{AT}$ <11 mL/kg per minute and $\dot{V}E$ versus $\dot{V}CO_2$ slope >34 was the best predictor of 6-month mortality (RR=5.1, $P=0.001$).

Conclusions—$\dot{V}O_2\text{AT}$ of <11 mL/kg per minute and slope of $\dot{V}E$ versus $\dot{V}CO_2$ >34, combined, better identified patients at high risk for early death from CHF than did peak $\dot{V}O_2$ 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 $\beta$-blockers, 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 $\dot{V}O_2$ was found to predict survival in patients with CHF. Mancini et al reported that patients with heart failure with a peak $\dot{V}O_2$ >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 $\dot{V}O_2$ in the evaluation for heart transplantation. The 24th Bethesda Conference for Cardiac Transplantation listed peak $\dot{V}O_2$<10 mL/kg per minute with achievement of anaerobic metabolism as an accepted indication for heart transplantation. Patients with a peak $\dot{V}O_2$ ≤14 mL/kg per minute and major limitation of daily activities were also transplantation candidates.

Peak $\dot{V}O_2$ might be underestimated because of reduced patient motivation as well as premature termination of exercise by the examiner. The anaerobic threshold ($\dot{V}O_2\text{AT}$) measures the sustainable $O_2$ 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. However, data showing its prognostic value in CHF do not yet exist. Recently, ventilatory efficiency, measured as the slope of $\dot{V}E$ versus $\dot{V}CO_2$ below the ventilatory compensation point for
exercise metabolic acidosis, was found to be a reliable predictor of prognosis in patients with CHF.18,19 As with \( \dot{V}O_2 \) 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 \( \dot{V}O_2 \) AT, of \( V_E \) versus \( VCO_2 \) 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 \( \dot{V}O_2 \) /kg.

**Methods**

**Patients**

The study included 223 consecutive patients with CHF referred to the Herzcentrum 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 Herzcentrum 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.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 (\( \dot{V}O_2 \)), carbon dioxide output (\( \dot{V}CO_2 \)), tidal volume (\( V_T \)), and breathing rate were measured. Blood gases (\( PaO_2 \), \( PaCO_2 \)) 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 (\( V_E \)), respiratory exchange ratio (\( VCO_2/\dot{V}O_2 \)), the \( O_2 \)-pulse (\( \dot{V}O_2/HR \)), and the ventilatory equivalents for \( O_2 \) and \( CO_2 \) (\( \dot{V}E/\dot{V}O_2 \), \( \dot{V}E/\dot{V}CO_2 \)) were calculated. Peak \( \dot{V}O_2 \) was determined as the highest \( \dot{V}O_2 \) achieved during exercise.

The anaerobic threshold (\( \dot{V}O_2 \text{AT} \)) was measured by the V-slope method.21 Typical changes in ventilatory equivalents and end-tidal gas concentrations (PETO2 and PETCO2) were examined to search for agreement in cases that were questionable with regard to the precise \( \dot{V}O_2 \) AT value. Predicted peak \( \dot{V}O_2 \) was determined by using the regression equations of Wasserman et al.13 The \( V_E \) versus \( VCO_2 \) 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 \( \dot{V}O_2 \) of \(<14 \text{ mL/kg per minute}^6\) or \(<50\%\text{normal}^{14} \). \( \dot{V}O_2 \) AT <11 mL/kg per minute,22-24 and a \( V_E \) versus \( VCO_2 \) slope >3418 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±1 SD. Discrete variables are shown as absolute values and/or percentages ± SD. Simple linear regression analysis was used to examine \( V_E \) versus \( VCO_2 \) slope as a function of peak \( \dot{V}O_2 \) and \( \dot{V}O_2 \text{AT} \). \( \chi^2 \) 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 \( V_E \) versus \( VCO_2 \) slope, peak \( \dot{V}O_2 \), \( \dot{V}O_2 \text{AT} \), 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%). LV EF was reduced to 28.7±8.1%; the left ventricular end-diastolic diameter was 65±7 mm. All patients had symptomatic heart failure, with a mean NYHA class of 2.1±0.7. The medical
treatment included ACE inhibitors in 95%, β-blockers in 43%, diuretics in 71%, digitalis in 69%, aspirin in 31%, and anticoagulants in 38% of the patients. Twenty patients (9%) had pacemakers and another 36 patients (16%) had an implanted cardioverter-defibrillator (ICD).

**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 underwent heart transplantation. The clinical characteristics of the survivors and nonsurvivors are presented in Table 1. The nonsurvivors were similar to the survivors in sex, body mass index, and in the cause of CHF but were older, more symptomatic, and had a lower LVEF (Table 1).

**Lung Function Test**

The mean vital capacity (VC) of all patients was 88% of predicted with a normal FEV1/VC ratio (Table 2). The nonsurvivors showed a more restrictive pattern expressed by a lower VC than survivors. The nonsurvivors had a slightly lower average PaCO2 at rest and at peak exercise compared with survivors. Dead space fractions of Ve (Vd/Vt) were increased to 0.62 and 0.49, during rest and peak exercise, respectively (Table 2).

<table>
<thead>
<tr>
<th>TABLE 2. Lung Function, Blood Gases, Exercise Characteristics of the Study Population (n=223), and Differences Between Survivors and Nonsurvivors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung Function/Exercise Characteristics</td>
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<tr>
<td>-------------------------------------------------------------</td>
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<tr>
<td>Lung function: VC, % normal</td>
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<tr>
<td>FEV1/L1 s</td>
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<tr>
<td>FEV1/VC, %</td>
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<tr>
<td>Blood gases: PacO2 peak exercise, mm Hg</td>
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<tr>
<td>PacO2 rest, mm Hg</td>
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<tr>
<td>PacO2 peak exercise, mm Hg</td>
</tr>
<tr>
<td>Exercise data: Heart rate at rest, bpm</td>
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<tr>
<td>Heart rate at peak exercise, bpm</td>
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<tr>
<td>Maximal work load, W</td>
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<tr>
<td>PeakVO2, mL/kg per minute</td>
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<tr>
<td>PeakVO2, % predicted</td>
</tr>
<tr>
<td>VO2AT, mL/kg per minute</td>
</tr>
<tr>
<td>Peak VO2-pulse, mL/min per beat</td>
</tr>
<tr>
<td>Ve peak exercise, L/min</td>
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<tr>
<td>Ve vs VCO2 slope</td>
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<tr>
<td>Vd/Vt at rest</td>
</tr>
<tr>
<td>Vd/Vt peak exercise</td>
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<tr>
<td>RER peak exercise</td>
</tr>
</tbody>
</table>

*Probability value for differences between survivors and nonsurvivors.

**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 O2-pulse was lower in nonsurvivors. Ve at maximal exercise was lower in nonsurvivors because of their lower maximal work rate.

**Cardiopulmonary Predictors of Long-Term Mortality**

Peak VO2 ≤14, peak VO2 ≤50% normal, Ve versus VCO2 slope >34, and VO2AT <11 were significant predictors of death in CHF during the median follow-up of 644 days (Figure 1). Peak VO2 ≤14 and VO2AT <11 were more predictive, with odds ratios of 3.9 and 3.7 than the percent of predicted peak VO2 and the Ve versus VCO2 slope with odds ratios of 2.5 and 3.0, respectively. VO2AT <11 identified 4 additional nonsurvivors not identified by peak VO2 ≤14 (Figure 2). In patients with peak VO2 ≤14 and Ve versus VCO2 slope >34, the increased risk of death was 6.1 times (Figure 1); whereas the combination of Ve versus VCO2 slope >34 and VO2AT <11 increased risk of death 7.0 times during follow-up (P<0.001, Figure 1). Thirty-six of 46 nonsurvivors...
had VO₂AT <11 and 31 of 46 had a VE versus VCO₂ slope >34. Only 6 of 46 nonsurvivors had nonpathological values for either VO₂AT <11 and the VE versus VCO₂ 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 VO₂ ≤50% of predicted was not predictive of early death (Figure 5). Patients with peak VO₂ ≤14 had a >3-fold risk, whereas patients with VE versus VCO₂ slope >34 had a 4.8-fold risk of early death. However, the best single predictor of early death was VO₂AT <11 with a 5.3-fold-increased risk (Figure 5). Combining peak VO₂ ≤14 with VE versus VCO₂ slope >34, the increased risk of death was 6.1-fold; the combination of VE versus VCO₂ slope >34 and VO₂AT <11 was 9.6-fold (P<0.001, Figure 5). Patients who had both VO₂AT <11 and VE versus VCO₂ slope >34 showed a 6-month mortality rate of 21.7% compared with only 2.6% in patients without these changes.

Discussion

Study Findings
To our knowledge, this is the first prospective study of cardiopulmonary exercise data in consecutive patients with CHF to compare VO₂AT <11 as a predictor of early 6-month mortality with the established prognostic parameters of peak VO₂ ≤14 or peak VO₂ ≤50% predicted. By itself and in combination with VE versus VCO₂ 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. Most studies on the prognostic value of cardiopulmonary exercise parameters were conducted before \(\beta\)-adrenergic blockers were shown to be beneficial in CHF. Recent published data reported \(\beta\)-adrenergic blocker use in only 31% of patients with CHF. Forty-three percent of our study population were taking long-term \(\beta\)-adrenergic blocker therapy. However, the role of \(\beta\)-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 \(V_O2\) related to body weight has been the most widely used parameter to predict survival in patients with CHF. A value of 14 mL/kg per minute was recommended for selecting potential candidates for heart transplantation. Patients with peak \(V_O2\) < 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 \(V_O2\), as previously described. We confirmed that a peak \(V_O2\) ≤ 14 mL/kg per minute and the percent predicted value might be interchangeable. In our study population, peak \(V_O2\) ≤ 50% normal could identify patients at increased risk for long-term but not 6-month mortality.

Chua et al\(^{18}\) and Kleber et al\(^{19}\) demonstrated the prognostic value of the ventilatory efficiency (Ve versus V\(CO_2\) slope) during exercise. We used the cutoff value of Ve versus V\(CO_2\) 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. Stevenson\(^{11}\) reported that \(V_O2\) AT was essentially interchangeable with peak \(V_O2\). 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 (V_O2) ≤ 14 mL/kg per minute</td>
<td>2.9</td>
<td>1.5–5.4</td>
<td>0.002</td>
</tr>
<tr>
<td>Peak (V_O2) ≤ 10 mL/kg per minute</td>
<td>2.1</td>
<td>1.1–4.3</td>
<td>0.04</td>
</tr>
<tr>
<td>Peak (V_O2) ≤ 50% normal</td>
<td>2.0</td>
<td>1.1–3.7</td>
<td>0.03</td>
</tr>
<tr>
<td>(V_O2) 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 V(CO_2) slope &gt; 34</td>
<td>2.7</td>
<td>1.5–5.1</td>
<td>0.001</td>
</tr>
<tr>
<td>Peak (V_O2) ≤ 14 + (V_O2) AT &lt; 11</td>
<td>3.2</td>
<td>1.5–6.7</td>
<td>0.003</td>
</tr>
<tr>
<td>Peak (V_O2) ≤ 14 + Ve vs V(CO_2) slope &gt; 34</td>
<td>4.5</td>
<td>2.1–10.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>(V_O2) AT &lt; 11 + Ve vs V(CO_2) 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 and to studies of cardiopulmonary exercise testing in preoperative evaluation of elderly patients by Older and Hall, we have chosen V̇O₂AT <11 as a cutoff value for high risk. We compared the V̇O₂AT with the peak V̇O₂ to determine their respective prognostic strengths for early (6 months) and long-term (2 years) mortality. V̇O₂AT <11 identified additional patients to be at high risk. This parameter was as good as peak V̇O₂ 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, V̇O₂AT <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 V̇E versus V̇CO₂ slope as for V̇O₂AT (Table 3). Both parameters can be derived simultaneously from the same exercise test. In contrast to peak V̇O₂, which is strongly dependent on patient motivation to perform a maximal effort exercise, V̇O₂AT and V̇E versus V̇CO₂ slope can be determined from a submaximal effort exercise test. We therefore combined V̇O₂AT <11 with V̇E versus V̇CO₂ slope >34 for risk stratification. This combination surpassed all other parameters in their prognostic strength even after multivariable 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 β-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 V̇O₂AT for early and long-term mortality in CHF. The combination of V̇O₂AT <11 and the V̇E versus V̇CO₂ slope >34 better identifies patients at risk for early death from CHF than peak V̇O₂ who therefore should be considered as candidates for early heart transplantation.

References
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*Circulation.* 2002;106:3079-3084; originally published online November 18, 2002;
doi: 10.1161/01.CIR.0000041428.99427.06
*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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