Ventilatory and Heart Rate Responses to Exercise
Better Predictors of Heart Failure Mortality Than Peak Oxygen Consumption

Mark Robbins, MD; Gary Francis, MD; Fredric J. Pashkow, MD; Claire E. Snader, MA; Kathy Hoercher, RN; James B. Young, MD; Michael S. Lauer, MD

Background—An abnormally low chronotropic response and an abnormally high ventilatory response (Ve/VCO2) to exercise are common in patients with severe heart failure, but their relative prognostic impacts have not been well explored.

Methods and Results—Consecutive patients with heart failure referred for metabolic stress testing who were not taking β-blockers or intravenous inotropes (n=470) were followed for 1.5 years. The chronotropic index was calculated while peak VO2 and Ve/VCO2 were directly measured. Chronotropic index and peak VO2 were considered abnormal if in the lowest 25th percentiles of the patient cohort, whereas Ve/VCO2 was considered abnormal if in the highest 25th percentile. For comparative purposes, a group of 17 healthy controls underwent metabolic testing as well. Compared with controls, heart failure patients had markedly abnormal ventilatory and chronotropic responses to exercise. In the heart failure cohort, there were 71 deaths. In univariate analyses, predictors of death included high Ve/VCO2, low chronotropic index, low VO2, low resting systolic blood pressure, and older age. Nonparametric Kaplan-Meier plots demonstrated that by dividing the population according to peak Ve/VCO2 and peak VO2, it is possible to identify low, intermediate, and very high risk groups. In multivariate analyses, the only independent predictors of death were high Ve/VCO2 (adjusted relative risk [RR] 3.20, 95% CI 1.95 to 5.26, P<0.0001) and low chronotropic index (adjusted RR 1.94, 95% CI 1.18 to 3.19, P=0.0009).

Conclusions—The ventilatory and chronotropic responses to exercise are powerful and independent predictors of heart failure mortality. (Circulation. 1999;100:2411-2417.)

Key Words: heart failure ■ mortality ■ exercise ■ heart rate ■ ventilation

Currently 3.5 million people carry the diagnosis of heart failure in the United States, and the number is expected to increase to 6 million by the year 2030.1 As cardiac transplantation has become a viable treatment option for patients with end-stage disease, it has become more incumbent on physicians to acquire precise prognostic information in order to provide accurate risk stratification.2 Although several potential predictive variables have been studied, functional capacity, as defined by direct measurement of maximal oxygen consumption, has emerged as the most consistent and powerful predictor of mortality.3-5 Recently, reduced heart rate variability, as well as abnormal ventilatory and heart rate responses to exercise, have been found to be common in patients with severe heart failure.6-8 Whether they provide additional prognostic information, either alone or in combination, over peak oxygen consumption has not been well studied. Therefore, the purpose of this study was to carefully examine the predictive properties of the chronotropic and ventilatory responses to exercise among patients referred for exercise testing who manifest chronic heart failure.

Methods

Study Population

The heart failure study cohort consisted of consecutive adults aged 18 to 70 who suffered from chronic heart failure and were referred for metabolic stress testing as part of a heart transplant evaluation. Patients were excluded if taking beta-adrenergic blockers or intravenous inotropes. For comparative purposes, a control cohort of 17 healthy adults underwent metabolic stress testing as well.

Clinic Data

Before each metabolic stress test, a structured interview and chart review yielded data on demographics, left ventricular ejection fraction, medications, cause of heart failure, standard cardiac risk factors, and other comorbidities. The definition of hypertension was based on JNC V criteria,9 whereas chart review and use of hypoglycemic medications established the diagnosis of diabetes.
Table 1. Comparison of Selected Characteristics Between Healthy Controls and Heart Failure Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Controls (n=17)</th>
<th>Heart Failure (n=470)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>41±13</td>
<td>52±11</td>
</tr>
<tr>
<td>Female</td>
<td>7 (41%)</td>
<td>134 (29%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>2 (12%)</td>
<td>116 (25%)</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.8±0.1</td>
<td>1.7±0.1</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>80±18</td>
<td>83±18</td>
</tr>
<tr>
<td>Resting heart rate, bpm</td>
<td>67±11</td>
<td>85±18</td>
</tr>
<tr>
<td>Resting systolic blood pressure, mm Hg</td>
<td>123±17</td>
<td>111±18</td>
</tr>
<tr>
<td>Resting diastolic blood pressure, mm Hg</td>
<td>79±14</td>
<td>76±11</td>
</tr>
<tr>
<td>Peak oxygen consumption, mL·kg(^{-1})·min(^{-1})</td>
<td>32±8</td>
<td>18±6</td>
</tr>
<tr>
<td>Oxygen consumption at AT, mL·kg(^{-1})·min(^{-1})</td>
<td>19±7</td>
<td>13±7</td>
</tr>
<tr>
<td>Peak respiratory exchange ratio</td>
<td>1.17±0.12</td>
<td>1.14±0.09</td>
</tr>
<tr>
<td>Peak heart rate, bpm</td>
<td>172±19</td>
<td>144±25</td>
</tr>
<tr>
<td>Peak systolic blood pressure, mm Hg</td>
<td>169±29</td>
<td>140±32</td>
</tr>
<tr>
<td>Chronotropic index</td>
<td>0.94±0.16</td>
<td>0.71±0.28</td>
</tr>
<tr>
<td>Peak minute ventilation, L/min</td>
<td>91±29</td>
<td>64±20</td>
</tr>
<tr>
<td>Peak respiratory rate, breaths/min</td>
<td>39±17</td>
<td>38±9</td>
</tr>
<tr>
<td>Peak tidal volume, L</td>
<td>2.4±0.8</td>
<td>1.7±0.5</td>
</tr>
<tr>
<td>Ve/Vco₂</td>
<td>31.0±3.3</td>
<td>39.6±9.9</td>
</tr>
</tbody>
</table>

AT indicates anaerobic threshold.

Exercise Testing
Symptom-limited metabolic stress testing was performed according to the Naughton protocol and recorded on a MedGraphics cardiopulmonary system. Measurements of oxygen consumption (V\(\text{O}_2\)), carbon dioxide production (V\(\text{CO}_2\)), heart rate, minute ventilation (VE), tidal volume (VT), end-tidal carbon dioxide tension (P\(\text{ETCO}_2\)), end tidal oxygen tension (P\(\text{ETO}_2\)), and respiratory rate were made after steady state at rest and every 30 seconds during exercise. Also, during each stage of exercise, data on symptoms, rhythm, blood pressure (by indirect sphygmomanometry), and ST segment changes were prospectively collected. The ventilatory response to exercise was defined as the value of Ve/Vco₂ at peak exercise. Anaerobic threshold was determined by V-slope method if possible, otherwise, by inspection of ventilatory equivalents. Patients were encouraged to exercise to a respiratory exchange ratio (ie, V\(\text{CO}_2\)/V\(\text{O}_2\)) ≥1.09.

Heart Rate Response to Exercise
Typically, the age-predicted maximum heart rate follows a linear regression equation, eg, 200 minus age in years. The problem with simply dividing peak heart rate by age-predicted maximum heart rate is that this value is significantly confounded by effects of age, resting heart rate, and most importantly, physical fitness. Wilkoff has described a method for describing the exercise heart rate response that takes advantage of the linear relation between exercise heart rate and metabolic work. Before exercise, a person has a certain metabolic reserve which is the difference between his peak oxygen consumption (or exercise capacity) and his rest oxygen consumption, typically 3.5 mL·kg\(^{-1}\)·min\(^{-1}\), or 1 metabolic equivalent (MET). As exercise progresses, that metabolic reserve is used up. Analogously, at rest there is a potential heart rate reserve, which is the difference between the peak attainable heart rate (as estimated, for example, by 220 minus age) and the resting heart rate. As exercise progresses heart rate reserve (HRR), like the metabolic reserve, is used up as well.

Thus, during any given stage of exercise, the percent metabolic reserve (MR) used can be expressed as:

\[ \% \text{MR used} = \left( \frac{(\text{METs}_{\text{stage}} - \text{METs}_{\text{rest}})}{(\text{METs}_{\text{peak}} - \text{METs}_{\text{rest}})} \right) \times 100 \]

Table 2. Baseline Characteristics of Heart Failure Patients According to Value of Peak Ve/Vco₂

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Ve/Vco₂ Normal (≤44.7)</th>
<th>Ve/Vco₂ Abnormal (&gt;44.7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>50±11</td>
<td>56±9</td>
</tr>
<tr>
<td>Female</td>
<td>108 (31)</td>
<td>26 (22)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>107 (30)</td>
<td>56 (47)</td>
</tr>
<tr>
<td>Smoking</td>
<td>81 (23)</td>
<td>35 (30)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>67 (19)</td>
<td>21 (18)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>131 (38)</td>
<td>43 (36)</td>
</tr>
<tr>
<td>Lipid lowering therapy</td>
<td>63 (18)</td>
<td>12 (10)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>277 (79)</td>
<td>102 (66)</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>298 (85)</td>
<td>105 (89)</td>
</tr>
<tr>
<td>Diuretic</td>
<td>269 (76)</td>
<td>104 (88)</td>
</tr>
<tr>
<td>Ca-channel blocker</td>
<td>26 (7.4)</td>
<td>3 (2.5)</td>
</tr>
<tr>
<td>Resting systolic blood pressure, mm Hg</td>
<td>113±18</td>
<td>105±16</td>
</tr>
<tr>
<td>Resting diastolic blood pressure, mm Hg</td>
<td>76±11</td>
<td>74±10</td>
</tr>
<tr>
<td>Resting heart rate, bpm</td>
<td>83±17</td>
<td>86±15</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>21 (7.0)</td>
<td>8 (6.6)</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>21±8</td>
<td>18±7</td>
</tr>
</tbody>
</table>

Values in parentheses are percentages. ACE indicates angiotensin converting enzyme.

In an analogous fashion, the percent HRR used at any given stage of exercise is:

\[ \% \text{HRR used} = \left( \frac{(\text{HR}_{\text{stage}} - \text{HR}_{\text{rest}})}{(220 - \text{age} - \text{HR}_{\text{rest}})} \right) \times 100 \]

In a group of healthy, nonhospitalized adults, a plot of heart rate reserve used to metabolic reserve used (% HRR used/% MR used) revealed a tight linear relationship with a slope of ~1 and a 95% CI of 0.8 to 1.3. This chronotropic index accounts for age, resting heart rate, and functional capacity, and its value is independent of the stage of exercise considered or the protocol used. For the current study, peak exercise values were used.

End Points
The primary end point was death due to any cause; patients who underwent transplantation were censored on their transplant date.

Table 3. Exercise Characteristics of Heart Failure Patients According to the Value of Peak Ve/Vco₂

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Ve/Vco₂ Normal (≤44.7)</th>
<th>Ve/Vco₂ Abnormal (&gt;44.7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak (\text{VO}_2), mL·kg(^{-1})·min(^{-1})</td>
<td>20±6</td>
<td>13±5</td>
</tr>
<tr>
<td>(\text{V}_0) AT, mL·kg(^{-1})·min(^{-1})</td>
<td>14±7</td>
<td>10±3</td>
</tr>
<tr>
<td>Peak respiratory exchange ratio</td>
<td>1.14±0.01</td>
<td>1.14±0.01</td>
</tr>
<tr>
<td>Peak heart rate, bpm</td>
<td>148±25</td>
<td>130±20</td>
</tr>
<tr>
<td>Peak systolic blood pressure, mm Hg</td>
<td>147±31</td>
<td>119±25</td>
</tr>
<tr>
<td>Chronotropic index</td>
<td>0.76±0.3</td>
<td>0.55±0.2</td>
</tr>
<tr>
<td>Peak Ve, L/min</td>
<td>66±21</td>
<td>61±16</td>
</tr>
<tr>
<td>Peak respiratory rate, bpm</td>
<td>37±8</td>
<td>40±8</td>
</tr>
<tr>
<td>Resting Ve/Vco₂*</td>
<td>42±6</td>
<td>52±7</td>
</tr>
<tr>
<td>AT Ve/Vco₂*</td>
<td>34±5</td>
<td>47±7</td>
</tr>
</tbody>
</table>

\(\text{V}_0\) AT indicates oxygen consumption at anaerobic threshold; Ve, minute ventilation; \(\text{V}_0\), carbon dioxide production; and peak \(\text{V}_0\), peak oxygen consumption.

*Among patients where anaerobic threshold could be determined (n=406).
Vital status was assessed by (1) interrogation of the hospital information system, (2) phone calls to patients, next of kin, or primary physicians, and (3) search of the social security master files. Vital status was confirmed in >98% of patients.

**Statistical Analyses**

Cut-off values for high \(\dot{V}E/\dot{V}CO_2\), low chronotropic index, low peak \(\dot{V}O_2\), low ejection fraction, short stature, low body weight, resting tachycardia, and low resting blood pressure were based on 75th or 25th percentiles as appropriate. The 75th and 25th percentile values were derived from the heart failure cohort. For descriptive purposes, baseline and exercise characteristics were divided according to percentiles 13.9 and 21.4 mL kg\(^{-1}\) min\(^{-1}\). A plot of estimated 18-month survivals for different variables thought to be related to death were analyzed using the Kaplan-Meier approach with formal testing by the log-rank test and univariate Cox regression analyses.

**TABLE 4. Univariate Predictors of Death (n=71) Among Heart Failure Patients**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline Mortality*, %</th>
<th>Relative Risk (95% CI)</th>
<th>(\chi^2)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (\dot{V}E/\dot{V}CO_2) (≥44.7)</td>
<td>10</td>
<td>3.96 (2.48–6.31)</td>
<td>33</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Low chronotropic index (≤0.51)</td>
<td>11</td>
<td>2.82 (1.76–4.50)</td>
<td>18</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Low peak (\dot{V}O_2) (≤13.9)</td>
<td>11</td>
<td>2.72 (1.70–4.35)</td>
<td>17</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Low resting SBP (≤98 mm Hg)</td>
<td>12</td>
<td>2.10 (1.31–3.36)</td>
<td>10</td>
<td>0.0019</td>
</tr>
<tr>
<td>Low ejection fraction (≤15%)</td>
<td>12</td>
<td>2.18 (1.32–3.59)</td>
<td>9</td>
<td>0.0022</td>
</tr>
<tr>
<td>Older age (≥61 y)</td>
<td>13</td>
<td>1.97 (1.22–3.19)</td>
<td>8</td>
<td>0.0055</td>
</tr>
<tr>
<td>Female</td>
<td>18</td>
<td>0.49 (0.26–0.92)</td>
<td>5</td>
<td>0.03</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>13</td>
<td>1.57 (0.98–2.51)</td>
<td>4</td>
<td>0.06</td>
</tr>
<tr>
<td>Diabetes</td>
<td>14</td>
<td>1.51 (0.88–2.57)</td>
<td>3</td>
<td>0.133</td>
</tr>
<tr>
<td>Smoker</td>
<td>14</td>
<td>1.42 (0.86–2.35)</td>
<td>2</td>
<td>0.17</td>
</tr>
<tr>
<td>Shorter stature (≤167 cm)</td>
<td>16</td>
<td>0.69 (0.39–1.24)</td>
<td>2</td>
<td>0.22</td>
</tr>
<tr>
<td>Hypertension</td>
<td>14</td>
<td>1.30 (0.82–2.09)</td>
<td>1</td>
<td>0.27</td>
</tr>
<tr>
<td>High resting heart rate (≥96 bpm)</td>
<td>15</td>
<td>0.93 (0.55–1.59)</td>
<td>&lt;1</td>
<td>0.80</td>
</tr>
<tr>
<td>Low weight (≤71 kg)</td>
<td>16</td>
<td>0.93 (0.54–1.61)</td>
<td>&lt;1</td>
<td>0.81</td>
</tr>
</tbody>
</table>

\(\dot{V}E/\dot{V}CO_2\) indicates blood pressure. Relative risks and CIs were derived from univariate Cox regression analyses.

**Results**

**Baseline Characteristics**

There were 470 heart failure patients eligible for analyses (72% men, age 52±11 years, ejection fraction 21±8%, median peak \(\dot{V}O_2\) 17.2 mL kg\(^{-1}\) min\(^{-1}\) with 25th and 75th percentile 13.9 and 21.4 mL kg\(^{-1}\) min\(^{-1}\), respectively). A respiratory exchange ratio of ≥1.09 was reached in 79% of the patients, whereas 90% reached a value of ≥1.02. The majority of patients (65%) had a nonischemic cause of left ventricular dysfunction. Hypertension and atrial fibrillation were derived from univariate Cox regression analyses. The key variables of interest, namely \(\dot{V}E/\dot{V}CO_2\), chronotropic index, and peak \(\dot{V}O_2\), were assessed using both categorical and continuous approaches; for continuous approaches, logarithmic and inverse transformations were analyzed and found not to improve prediction of death. To avoid model overfitting, no more than 1 covariate per 10 outcome events were considered in regression models.

The ventilatory response to exercise is dependent on ventilatory drive, physiological dead space, and patient motivation to drive exercise beyond the anaerobic threshold. In order to eliminate potential confounding from the last factor, supplementary analyses were performed relating values of \(\dot{V}E/\dot{V}CO_2\) at rest and at anaerobic threshold. These analyses were confined to the 406 patients in whom anaerobic threshold could be determined. Pearson correlation analyses were used to assess the association between peak and submaximal values.

To analyze the association of peak \(\dot{V}E/\dot{V}CO_2\) and mortality in a continuous manner, a wholly parametric approach was used. One phase of constant hazard was identified indicating that an exponential model worked well. Modeling of peak \(\dot{V}E/\dot{V}CO_2\) and mortality included testing of logarithmic, threshold, inverse, and quadratic transformations after inspection of log odds of risk across quintiles of peak \(\dot{V}E/\dot{V}CO_2\). A plot of estimated 18-month survivals for different conditions was constructed along with one standard error confidence limits.

All analyses were performed using the SAS 6.12 system (SAS, Inc). Statistical comparisons were considered significant for probability value ≤0.01. Parametric hazards analyses were performed using PROC HAZARD and PROC HAZPRED (available from ftp://uabcvsr.cvsr.uab.edu).

**Figure 1.** Kaplan-Meier plot relating survival to \(\dot{V}E/\dot{V}CO_2\). For numbers in parentheses, numerators refer to number of deaths and denominators, number of patients within each subset.
were present in 38% and 6% of patients, respectively. Most patients were receiving standard therapy with angiotensin-converting enzyme inhibitors (86%), digoxin (81%), and diuretics (79%). Only 6% of patients were taking calcium channel blockers.

Compared with 17 healthy controls (Table 1), the heart failure patients had markedly higher resting heart rate and peak $V_{\dot{E}}/V_{\dot{CO}_2}$ and markedly lower peak $V_{\dot{O}_2}$, peak heart rate, peak systolic blood pressure, and chronotropic index. Of note, the respiratory exchange ratios and the peak respiratory rates were similar in the 2 groups.

Baseline characteristics according to value of peak $V_{\dot{E}}/V_{\dot{CO}_2}$ are summarized in Table 2. Patients who had an abnormally high $V_{\dot{E}}/V_{\dot{CO}_2}$ were more likely to be older, have a history of coronary artery disease, and have lower resting systolic blood pressure, higher resting heart rate, and a lower ejection fraction. There were no marked differences between the 2 groups with respect to history of smoking, hypertension, diabetes, or atrial fibrillation.

Baseline exercise characteristics according to peak $V_{\dot{E}}/V_{\dot{CO}_2}$ are summarized in Table 3. Patients with an abnormal $V_{\dot{E}}/V_{\dot{CO}_2}$ had a lower exercise capacity (lower peak $V_{\dot{O}_2}$ and $V_{\dot{O}_2}$ at anaerobic threshold), a lower peak systolic blood pressure and heart rate, as well as a lower chronotropic index and lower peak $V_{\dot{E}}$. There was no difference in the respiratory exchange ratio between the 2 groups.

**Correlation Analyses**

Peak $V_{\dot{O}_2}$ was found to have at least a moderate correlation with $V_{\dot{E}}/V_{\dot{CO}_2}$ ($r = -0.64$) and chronotropic index ($r = 0.58$). The correlation was more modest between $V_{\dot{E}}/V_{\dot{CO}_2}$ and chronotropic index ($r = -0.39$). Left ventricular ejection fraction had very weak correlations with $V_{\dot{E}}/V_{\dot{CO}_2}$ ($r = -0.23$), chronotropic index ($r = 0.09$), and peak $V_{\dot{O}_2}$ ($r = 0.15$).

**Predictors of Mortality**

Univariate predictors of death are found in Table 4. An abnormally high peak $V_{\dot{E}}/V_{\dot{CO}_2}$ ($\geq 44.7$) was the strongest predictor of death. Analyses of the Kaplan-Meier survival curves (Figure 1) revealed a 1.5-year survival rate of 90% for those with a normal peak $V_{\dot{E}}/V_{\dot{CO}_2}$, compared with only 67% for those with an abnormal value. A low chronotropic index and a low peak $V_{\dot{O}_2}$ also predicted higher mortality rates (Table 4, Figures 2 and 3). Resting systolic blood pressure, low ejection fraction, and older age were weaker predictors of death.

**Combination of Risks and Mortality**

When evaluating the significance of any combination of an abnormally high $V_{\dot{E}}/V_{\dot{CO}_2}$, low peak $V_{\dot{O}_2}$, and low chronotropic index, an abnormally high $V_{\dot{E}}/V_{\dot{CO}_2}$ combined with a low chronotropic index was associated with the highest risk of death (Figure 4). Combinations of an abnormally high $V_{\dot{E}}/V_{\dot{CO}_2}$ and a low peak $V_{\dot{O}_2}$ (Figure 5) and a low chronotropic index and a low peak $V_{\dot{O}_2}$ (Figure 6) also identified groups at very high and relatively low risks for death.

**Multivariate Analyses**

Results of stepwise multivariate proportional hazards analyses are summarized in Table 5. After adjusting for low peak $V_{\dot{O}_2}$, age, sex, history of coronary artery disease, and resting systolic blood pressure, only an abnormally high $V_{\dot{E}}/V_{\dot{CO}_2}$ and a low chronotropic index remained independently pre-
dictive of death. When peak $V_\text{O}_2$ was forced into the regression model, again only a high $V_\text{E}/V_\text{CO}_2$ and a low chronotropic index were predictive of death. When covariates were analyzed in a continuous manner, only $V_\text{E}/V_\text{CO}_2$, chronotropic index, and resting systolic blood pressure were predictive; peak $V_\text{O}_2$ was not associated with death.

When transplanted patients were excluded from the analyses, multivariate models yielded essentially identical results. There were no significant interactions found between any of the variables considered for prediction of mortality.

**Associations of Resting and Submaximal $V_\text{E}/V_\text{CO}_2$ With Mortality**

Among the 406 patients for whom anaerobic threshold could be determined, resting and anaerobic threshold values of $V_\text{E}/V_\text{CO}_2$ were higher when the peak value was abnormally high (Table 3). There was a strong correlation between peak and anaerobic threshold values ($r=0.86$) with a less strong correlation with resting values ($r=0.66$). Resting, anaerobic threshold, and peak values of $V_\text{E}/V_\text{CO}_2$ were all associated with mortality (Table 6), with the anaerobic threshold value almost as strong a predictor as the peak value. After adjustment for potential confounders, the anaerobic threshold and peak values remained predictive of mortality (Table 6).

**Peak $V_\text{E}/V_\text{CO}_2$ as a Continuous Variable**

When considered as a continuous variable, peak $V_\text{E}/V_\text{CO}_2$ had a range of 15 to 84 with 5th, 25th, 50th, 75th, and 95th percentile values of 27, 33, 38, 45, and 58, respectively. A parametric model found that independent predictors of mortality included peak $V_\text{E}/V_\text{CO}_2$ ($P=0.02$), resting systolic blood pressure ($P=0.02$), and male gender ($P=0.03$). Weaker predictors were chronotropic index ($P=0.06$) and peak $V_\text{O}_2$ ($0.07$). A plot of estimated 18-month survival according to values of peak $V_\text{E}/V_\text{CO}_2$ and peak $V_\text{O}_2$ is shown in Figure 7. Of note, a threshold effect was noted whereby the mortality impact of peak $V_\text{E}/V_\text{CO}_2$ becomes particularly marked at values exceeding 40 to 45.

**Discussion**

**Principal Findings**

Abnormal ventilatory and chronotropic responses to exercise were powerful and independent predictors of mortality. Al-though both a high $V_\text{E}/V_\text{CO}_2$ and a low chronotropic index were associated with a low peak $V_\text{O}_2$, in both univariate and multivariate analyses, these 2 values emerged as substantially stronger correlates of death.

There were 2 other findings of note. First, the value of $V_\text{E}/V_\text{CO}_2$ obtained at submaximal exercise, namely at anaerobic threshold, was almost as strong an independent predictor of mortality as the peak value. Second, a parametric analysis of peak $V_\text{E}/V_\text{CO}_2$ considered as a continuous variable revealed a threshold pattern, in which the mortality impact increased markedly at values exceeding 40 to 45.

**Previous Findings**

Several groups have reported that patients with severe heart failure manifest an impaired heart rate variability at rest\textsuperscript{16} and...
TABLE 6. Resting, Submaximal, and Maximal $\dot{V}_E/\dot{V}_{CO_2}$ and Mortality Among Patients Who Had an Anaerobic Threshold That Could Be Determined

<table>
<thead>
<tr>
<th>$\dot{V}<em>E/\dot{V}</em>{CO_2}$</th>
<th>Relative Risk (95% CI)</th>
<th>$\chi^2$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted models*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>1.55 (1.23–1.94)</td>
<td>14</td>
<td>0.0002</td>
</tr>
<tr>
<td>Anaerobic threshold</td>
<td>1.83 (1.50–2.25)</td>
<td>34</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Peak exercise</td>
<td>1.89 (1.54–2.32)</td>
<td>38</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Adjusted models†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>1.21 (0.95–1.56)</td>
<td>2</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Anaerobic threshold</td>
<td>1.45 (1.10–1.90)</td>
<td>7</td>
<td>0.009</td>
</tr>
<tr>
<td>Peak exercise</td>
<td>1.53 (1.14–2.06)</td>
<td>8</td>
<td>0.005</td>
</tr>
</tbody>
</table>

*Results of univariate Cox regression analyses. Relative risks and CIs refer to 1-SD increases of $\dot{V}_E/\dot{V}_{CO_2}$ at rest, anaerobic threshold, and peak exercise. †Results of multivariate Cox regression analyses adjusted for age, sex, presence of ischemic heart disease, chronotropic index, and peak oxygen consumption.

Possible Mechanisms

The mechanisms underlying an abnormally high $\dot{V}_E/\dot{V}_{CO_2}$ in patients with heart failure are thought to be multifactorial and have been reported to include abnormalities among the following: central neurogenic drive, central chemoreceptors, cardiac mechanoreceptors, muscle ergoreceptors, anatomical and physiological dead space, and peripheral chemoreceptors. The $\dot{V}_E/\dot{V}_{CO_2}$ value is also reported to be independent of motivation with little change in value at 30%, 60%, and 100% of exercise capacity. In the present study, the prognostic superiority of $\dot{V}_E/\dot{V}_{CO_2}$ over peak $V_O_2$ may reflect the ability of this value to exclude those patients with a falsely low peak $V_O_2$ secondary to a lack of motivation or peripheral skeletal muscle dysfunction. In this regard, it is noteworthy that anaerobic threshold values of $\dot{V}_E/\dot{V}_{CO_2}$ were closely correlated with peak values and were almost as strongly predictive of death. Alternatively, it is possible that the underlying abnormalities of autonomic dysfunction associated with both abnormal ventilatory and chronotropic responses to exercise are distinct and more closely related to outcome.

It is noteworthy that peak respiratory rates in heart failure patients were similar to those of controls. This suggests that elevated levels of peak $\dot{V}_E/\dot{V}_{CO_2}$ in patients with severe heart failure may be due more to increased dead space rather than to abnormalities of ventilatory drive. Thus, $\dot{V}_E/\dot{V}_{CO_2}$ may be a better predictor of mortality as decreased cardiac output and elevated diastolic filling pressures may directly cause increased dead space in the form of interstitial edema and pulmonary endothelial dysfunction, whereas peak $V_O_2$ is a function of either central or peripheral abnormalities.

Limitations

The follow-up period for our study was relatively short; we are unable to comment on the effects of the ventilatory and chronotropic responses to exercise over >2 years of follow-up. Ejection fraction data were not obtained in a uniform manner among all patients; nonetheless, ejection fraction emerged as a relatively weaker predictor of outcome.

Another concern is that physicians would respond to low peak $V_O_2$ by listing patients for transplantation, thereby attenuating the association between peak $V_O_2$ and death. Peak $\dot{V}_E/\dot{V}_{CO_2}$ values were not considered in clinical decision-making at the time these patients were evaluated. When we excluded the 46 patients who were censored because of transplantation, the associations relating ventilatory and chronotropic responses to mortality were unchanged.
Conclusions
An abnormally high $\text{VE/VA}_{\text{CO}_2}$ and an abnormally low chronotropic index are both strong predictors of death among heart failure patients; their prognostic significance is independent of peak $\text{VO}_2$. Future research should focus on: (1) the influence of standard medical therapy (digoxin, ACE inhibitors, and diuretics), as well as, burgeoning therapies (β-adrenergic blockers, aldosterone inhibitors, and central active sympahtoinhibitory agents) on chronotropic response and $\text{VE/VA}_{\text{CO}_2}$, and (2) how best to routinely incorporate chronotropic index and $\text{VE/VA}_{\text{CO}_2}$ into heart failure staging and cardiac transplant evaluations.

References
Ventilatory and Heart Rate Responses to Exercise: Better Predictors of Heart Failure Mortality Than Peak Oxygen Consumption
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Circulation. 1999;100:2411-2417
doi: 10.1161/01.CIR.100.24.2411

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