Letter to the Editor

Combining peak oxygen consumption and ventilatory efficiency in the prognostic assessment of patients with heart failure☆

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Abstract

Exercise ventilatory efficiency (VE/VCO2 slope) and peak oxygen consumption (VO2) are strong mortality predictors in patients with heart failure and we combined these 2 variables’ beta coefficients from Cox regression to investigate a new prognostic index. Average follow-up was 3.8±1.8 years for 355 patients (72% male, 51±10 years). The beta coefficients from peak VO2 (17.3±5.0 ml·kg⁻¹·min⁻¹) and VE/VCO2 slope (37.0±9.0) constructed an exercise index defined as one half the peak VO2 subtracted from one fifth of the VE/VCO2 slope. The mean index was −1.14±3.79 and a more positive index was always associated with a higher probability of death. Patients with extremely poor prognoses were identified equally well by the index and by individual thresholds for peak VO2 (≤14 ml·kg⁻¹·min⁻¹) and of VE/VCO2 slope (≤40). In conclusion, the index did not add additional prognostic information in this cohort but it did display the prognostic superiority of VE/VCO2 slope.

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Keywords: Heart failure; Exercise testing; Oxygen consumption; Ventilatory efficiency

Cardiopulmonary exercise testing has routinely been used to assess prognosis from peak oxygen consumption (VO2), but VE/VCO2 slope is the most predictive exercise variable and it has yet to be integrated into clinical guidelines [1,2]. The combination of a low peak VO2 and a high VE/VCO2 slope identifies patients with a high mortality risk [3] and this combination has improved predictive ability above and beyond the contribution of either individual variable [4]. The purpose of this study was to develop a simple index that could be used clinically that incorporates both peak VO2 and VE/VCO2 slope to predict mortality in heart failure patients.

The University of Michigan IRB approved this project and patients signed informed consent. Every treadmill exercise test was conducted and analyzed by the same investigator. VE/VCO2 slope to peak exercise was determined with all of the available exercise data. Follow-up continued until at least 5 years had passed from the date of the exercise test.

The base model that best predicted mortality included: resting systolic blood pressure ≤100 mm Hg, resting heart rate ≥80 bpm, sex, etiology, peak VO2, VE/VCO2 slope, LVEF, sex, peak VO2, dichotomized SBP, dichotomized HR, and index.

Table 1A

<table>
<thead>
<tr>
<th>Comparison of the predictive ability of the index and other predictive variables from Cox regression in univariable analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>χ²</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Dichotomized HR (≥80 bpm)</td>
</tr>
<tr>
<td>LVEF (%)</td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Peak VO2</td>
</tr>
<tr>
<td>Dichotomized SBP (≤100 mm Hg)</td>
</tr>
<tr>
<td>VE/VCO2 slope</td>
</tr>
<tr>
<td>Index</td>
</tr>
</tbody>
</table>

☆ As presented at the American Heart Association scientific sessions in Dallas, Texas on November 14, 2005.
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Table 1B
Comparison of the predictive ability of the index and other predictive variables from Cox regression within the multivariable model

<table>
<thead>
<tr>
<th>Variable(s) added</th>
<th>$\chi^2$</th>
<th>Explained mortality variation ($R^2$) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak VO$_2$</td>
<td>69.9</td>
<td>18.0</td>
</tr>
<tr>
<td>VE/VCO$_2$ slope</td>
<td>83.5</td>
<td>21.1</td>
</tr>
<tr>
<td>Peak VO$_2$/VE/VCO$_2$ slope</td>
<td>91.3</td>
<td>22.8</td>
</tr>
<tr>
<td>Index</td>
<td>89.1</td>
<td>22.4</td>
</tr>
</tbody>
</table>

Including the variable(s) noted and adjusted for:

* Dichotomous resting systolic blood pressure ≤ 100 mm Hg.
* Dichotomous resting heart rate ≥ 80 bpm.
* Sex.
* Etiology.
* Left ventricular ejection fraction.

and left ventricular ejection fraction. Complete details of this patient cohort and the model derivation are previously reported [1].

A simple mathematical index of peak VO$_2$ and VE/VCO$_2$ slope was developed from the beta coefficients from Cox regression analyses that included both variables within the base model. The explained mortality variation (generalized $R^2$) [5] was determined to compare the prognostic ability of different models, and are reported in Tables 1A and 1B.

Peak VO$_2$ was 17.3±5.0 ml·kg$^{-1}$·min$^{-1}$ at an RER of 1.13±0.13 and a peak VE/VCO$_2$ slope of 37.0±9.0 in 355 patients (100 women) with an average age of 50.6±10.2 years. Follow-up events included 133 deaths, 12 urgent cardiac transplantations, and 17 censored elective cardiac transplantations. When entered into a Cox regression model, both VE/VCO$_2$ slope and peak VO$_2$ were significant mortality predictors and their beta coefficients were 0.022 and −0.058 respectively. Rounding these values for ease of clinical implementation, the index was defined as $1/5$ VE/VCO$_2$ Slope $−1/2$ VO$_2$; the mean index was $−1.14±3.79$.

The greater index was associated with increased mortality; the lowest quartile had 20% deaths and the highest quartile had 60% deaths. Patients above the 90th percentile of the index (>3.11) had 81% mortality. The worst quartile values for the index, peak VO$_2$, and VE/VCO$_2$ slope were 0.92, 13.7 ml·kg$^{-1}$·min$^{-1}$, and 41.3 respectively.

In univariable analysis, the VE/VCO$_2$ slope explained 11.1% of mortality. Based on the index, the addition of peak VO$_2$ to the VE/VCO$_2$ slope did not add much to the mortality prediction (a 0.1% increase). The majority of the mortality prediction came from VE/VCO$_2$ slope since peak VO$_2$ increased explained mortality variation from 21.1% to only 22.8%. When peak VO$_2$ and VE/VCO$_2$ slope were combined as the index, the explained mortality variation was the same as when they were both in the model independently.

The significance of this study is the presentation of the multivariable prognostication. In comparison to other studies involving cardiopulmonary exercise tests, the current study is well controlled and applicable to the clinical care of heart failure. We had a large sample size (355) with a long follow-up (at least 5 years) and a significant number of events (41%). All testing and data analyses were performed by the same investigator using the same equipment at the same location over a short period of time (21 months). We utilized rigorous statistical modeling that considered over 20 variables, their interactions, and threshold effects that resulted in the best possible multivariable model. [1] The major finding of this study is that the majority of the mortality prediction is explained by VE/VCO$_2$ slope, as indicated by the inability of the index to significantly improve the mortality prediction. Other studies [2,4,6] have made this conclusion but we were able to provide prognostic data in a simple manner using the generalized $R^2$ where we showed that peak VO$_2$ has a relatively weak contribution to mortality prediction within a multivariable model of heart failure patients, increasing prediction by only 1.7% (Table 1B). The index did not improve prognostication above the sum of its parts, but it can provide a single value in prognostic risk assessment. These data are useful since there are currently no recognized prognostic guidelines for the assessment of ventilatory efficiency in patients with heart failure.

References