Prognostic value of end-tidal carbon dioxide during exercise testing in heart failure
Ross Arenaa,⁎, Marco Guazzib, Jonathan Myersc

Abstract

Background: The partial pressure of end-tidal carbon dioxide production (PETCO2) at ventilatory threshold (VT) has been shown to be strongly correlated with cardiac output during exercise in patients with heart failure (HF), but few data are available regarding its prognostic utility.

Aims: The purpose of this study was to assess the ability of PETCO2 to predict cardiac-related events in a group of subjects with HF.

Methods: One hundred and thirty subjects diagnosed with compensated HF underwent cardiopulmonary exercise testing (CPX). Peak oxygen consumption (VO2), the minute ventilation–carbon dioxide production (VE/VCO2) slope and PETCO2 were determined.

Results: Receiver operating characteristic (ROC) curve analysis revealed that PETCO2 at the ventilatory threshold (VT) was a significant predictor of cardiac-related events (ROC area=0.82, p<0.001). The optimal PETCO2 at a VT threshold value for separating high (≤) and low (> risk groups was 36.1 mm Hg (77% sensitivity, 69% specificity). In a multivariate Cox regression analysis, PETCO2 at VT added significant predictive value to the VE/VCO2 slope and peak VO2.

Conclusion: These results indicate that PETCO2 during CPX is a significant predictor of cardiac-related events in patients with HF. Clinical assessment of this variable in patients with HF undergoing CPX may therefore be warranted.

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Keywords: Ventilatory expired gas; Hospitalization; Mortality

1. Introduction

Cardiopulmonary exercise testing (CPX) is commonly used to assess patients with heart failure (HF). Data obtained from CPX provides a wealth of diagnostic [1,2] and prognostic [3–5] information in the HF population. Peak oxygen consumption (VO2) remains the most frequently applied CPX variable in both research and clinical settings [6]. Other variables, such as the relationship between minute ventilation (VE) and carbon dioxide production (VCO2), have also been demonstrated to have prognostic value in recent years [7,8]. Given the wealth of information that can be gained from this assessment, further exploration of prognostically significant CPX variables is warranted.

The partial pressure of end-tidal carbon dioxide (PETCO2) is one such CPX variable that may possess prognostic value in the HF population. Matsumoto et al. [9] found that PETCO2 at the ventilatory threshold (VT) was significantly correlated with cardiac output at peak exercise in a group of subjects with HF. The sensitivity and specificity of PETCO2 (<38.5 mm Hg) to predict a lower cardiac output during exercise (cardiac index <5.11 l/min/m2 at peak exercise) were 76.5% and 75.0%, respectively. Tanabe et al. [10] likewise reported a significant correlation between PETCO2 and cardiac index at peak exercise in subjects diagnosed with HF. The results from these investigations indicate that PETCO2 closely reflects the cardiac output response to exercise and therefore may have diagnostic applications in patients with HF.
Table 1
Subject characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>130</td>
</tr>
<tr>
<td>Age (years)</td>
<td>49.2±14.5 a</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%) b</td>
<td>28.5±13.1 a</td>
</tr>
<tr>
<td>Resting PEtCO2 (mm Hg)</td>
<td>34.1±4.6 a</td>
</tr>
<tr>
<td>New York Heart Association Class (I/II/III)</td>
<td>27/52/51</td>
</tr>
<tr>
<td>Heart failure etiology (ischemic/non-ischemic)</td>
<td>54/76</td>
</tr>
<tr>
<td>ACE inhibitor (number of subjects)</td>
<td>99</td>
</tr>
<tr>
<td>Cardiac glycoside (number of subjects)</td>
<td>96</td>
</tr>
<tr>
<td>Diuretic (number of subjects)</td>
<td>108</td>
</tr>
<tr>
<td>Nitrate (number of subjects)</td>
<td>31</td>
</tr>
<tr>
<td>Beta-blocker (number of subjects)</td>
<td>59</td>
</tr>
</tbody>
</table>

a Standard deviation.
b Determined by two-dimensional echocardiography.

While there is evidence to demonstrate the diagnostic value of $P_{ET}CO_2$ during exercise in HF, studies on prognosis are lacking. Our group has recently completed a study demonstrating that a lower $P_{ET}CO_2$, obtained at rest, was a significant predictor of hospitalization/mortality in subjects with HF [11]. The purpose of the present study was to extend this analysis and examine the ability of $P_{ET}CO_2$ during exercise to predict cardiac-related hospitalization and mortality in a group of patients with HF.

2. Methods

One hundred and thirty consecutive subjects diagnosed with HF underwent a symptom-limited CPX between 5/15/97 and 7/26/04 at Virginia Commonwealth University Medical Center. All tests were conducted on an outpatient basis and written informed consent was obtained from all subjects prior to testing. Virginia Commonwealth University Institutional Review Board approval was obtained for those subjects undergoing an exercise test as part of a prospective research project and not as a standard of care. The investigation conforms with the principles outlined in the Declaration of Helsinki [12]. Subject and pharmacological characteristics are listed in Table 1.

Exclusion criteria consisted of diagnosed pulmonary disease (per physician examination and medical chart review), myocardial infarction within the past 6 months, signs and/or symptoms suggestive of decompensated HF and/or any orthopedic condition that would not allow the subject to ambulate on a treadmill. Inclusion criteria consisted of a previous diagnosis of HF that was in a compensated state at the time of testing and evidence of left ventricular dysfunction by echocardiogram.

3. Equipment calibration

Ventilatory expired gas analysis was obtained using a metabolic cart (Medgraphics CPX-D, Minneapolis, MN or Sensormedics Vmax29, Yorba Linda, CA). The oxygen and carbon dioxide sensors were calibrated using gases with known oxygen, nitrogen, and carbon dioxide concentrations prior to each test. The flow sensor was also calibrated before each test using a 3-l syringe.

4. Testing procedure and data collection

Symptom-limited CPX was conducted using a treadmill. The modified ramping protocol selected for testing consisted of approximately 2 ml O2 kg$^{-1}$ min$^{-1}$ increases in workload every 30 s [13–16]. Stage 1 began at 1.0 mile per hour (mph) and a 0% grade. Stages increased by 0.1 mph and 0.5% grade thereafter. Our group has found that this protocol minimizes the difference between estimated and measured VO2, indicating an acceptable kinetic response. Furthermore the gradual adjustment in workload appears to be well tolerated by patients with HF [16]. This treadmill protocol was used to test all subjects. Monitoring consisted of continuous 12-lead electrocardiography (Quinton 4000, Seattle, WA), manual blood pressure measurements approximately every third stage (90 s), heart rate recordings every stage via the electrocardiogram and rating of perceived exertion (Borg 15 grade scale) each stage. Test termination criteria consisted of patient request, ventricular tachycardia, ≥ 2 mm of horizontal or downsloping ST segment depression or a drop in systolic blood pressure ≥ 20 mm Hg during progressive exercise. A qualified exercise physiologist with physician supervision conducted each exercise test.

5. Data analysis

Oxygen consumption (ml kg$^{-1}$ min$^{-1}$), VCO2 (l/min) and VE (l/min) and $P_{ET}CO_2$ were collected throughout the exercise test. Resting $P_{ET}CO_2$ was also collected for 2 min prior to CPX in the seated position. Peak VO2 was expressed as the highest 10-s average value obtained during the last 30-s stage of the exercise test. The ventilatory equivalent method was used to determine $P_{ET}CO_2$ at the ventilatory threshold (VT) [17]. Ten-second averaged VE and VCO2 data, from the initiation of exercise to peak, were input into spreadsheet software (Microsoft Excel, Microsoft Corp., Bellevue, WA) to calculate the VE/VCO2 slope via least squares linear regression ($y = mx + b$, m = slope). Previous work by our group [18] and others [19] have shown this method of calculating the VE/VCO2 slope to be prognostically optimal. $P_{ET}CO_2$ was recorded at both VT and peak exercise as a 10-s averaged value. Change in $P_{ET}CO_2$ from rest to VT was also determined.

6. Endpoints

Subjects were followed for cardiac-related mortality and hospitalization for 1 year following CPX via medical chart review. Cardiac-related mortality was defined as death directly resulting from failure of the cardiac system. An example fitting this definition is sudden cardiac death. Cardiac-related hospitalization was defined as a hospital admission directly resulting from cardiac dysfunction.
requiring in-patient care to correct. An example fitting this definition is decompensated HF requiring intravenous inotropic and diuretic support. Any death or hospital admission with a cardiac-related discharge diagnosis, confirmed by diagnostic tests or autopsy, was considered an event. The most common causes of mortality, as per discharge diagnosis, were sudden cardiac death, myocardial infarction, and HF. The most common causes of hospitalization were decompensated HF and coronary artery disease. Subjects in whom mortality was of a non-cardiac etiology were treated as censored cases. For the purposes of this analysis, only the first event (hospitalization or death) was considered an event.

All subjects were followed as the HF program at Virginia Commonwealth University Medical Center. The subjects requiring hospitalization most frequently received their care at Virginia Commonwealth University Medical Center. In the rare event, subjects were hospitalized at another institution for inpatient care, a discharge note was sent to Virginia Commonwealth University Medical Center and maintained in the patient’s chart. All hospital discharge summaries and death certificates were obtained in the subject’s charts. We are therefore highly confident all events were captured for this group of subjects.

7. Statistical analysis

The mean and standard deviation were reported for key variables. Pearson product moment correlation was used to assess the relationship between measures of PETCO2 and age, LVEF, VO2, and the VE/VCO2 slope. Receiver operating characteristic (ROC) curve analysis was used to assess the ability of key resting and CPX continuous variables to predict cardiac-related events. For variables found to be statistically significant by ROC curve analysis, threshold values (highest combination of sensitivity and specificity) were determined. Univariate Cox regression analysis was used to determine the chi-square and hazard ratios for resting and CPX variables. Multivariate Cox regression analysis assessed the combined ability of key resting and CPX continuous variables to predict 1-year cardiac-related events. The forward stepwise method was used with entry and removal p-values for the multivariate analyses set at 0.05 and 0.10, respectively. The Cox-proportional hazard assumptions were checked for each variable with the log

### Table 3

<table>
<thead>
<tr>
<th>Variable</th>
<th>Age</th>
<th>LVEF</th>
<th>VE/CO2 slope</th>
<th>Peak VO2</th>
</tr>
</thead>
<tbody>
<tr>
<td>PETCO2 at VT</td>
<td>0.72</td>
<td>0.51</td>
<td>0.68–0.84</td>
<td>&gt;14.2</td>
</tr>
<tr>
<td>Change in PETCO2 from rest to VT</td>
<td>0.72</td>
<td>0.60</td>
<td>0.63–0.81</td>
<td>&gt;1.8</td>
</tr>
<tr>
<td>PETCO2 at peak</td>
<td>0.82</td>
<td>0.75</td>
<td>0.75–0.89</td>
<td>&gt;36.1</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.61</td>
<td>0.51</td>
<td>0.51–0.71</td>
<td>&gt;22.3</td>
</tr>
</tbody>
</table>

<log(survival function) plot. Kaplan–Meier analysis was used to assess differences in cardiac-related events for variables retained in the multivariate Cox regression analysis. The log-rank test was used to determine if the difference in event-free survival was significant between subjects falling into different categories. A statistical software program was used for all data analysis (SPSS 13.0 for Windows, Chicago, IL). All statistical tests with a p-value < 0.05 were considered significant.

8. Results

The primary reason for CPX termination was subject request secondary to volitional fatigue. No adverse events warranting premature test termination occurred. Mean values of CPX variables are listed in Table 2.

### Table 2

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>Standard deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak VO2 (ml O2 kg^-1 min^-1)</td>
<td>14.5</td>
<td>±5.2</td>
</tr>
<tr>
<td>Peak RER</td>
<td>1.05</td>
<td>±0.11</td>
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<tr>
<td>VE/CO2 slope</td>
<td>36.4</td>
<td>±9.3</td>
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<tr>
<td>Change in PETCO2 from rest to VT</td>
<td>3.1</td>
<td>±3.6</td>
</tr>
<tr>
<td>PETCO2 at peak (mm Hg)</td>
<td>34.1</td>
<td>±6.4</td>
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</tbody>
</table>

### Table 4

<table>
<thead>
<tr>
<th>Variable</th>
<th>ROC area</th>
<th>95% CI</th>
<th>Optimal threshold</th>
<th>Sensitivity/specifity</th>
</tr>
</thead>
<tbody>
<tr>
<td>VE/CO2 slope</td>
<td>0.83*</td>
<td>0.75–0.90</td>
<td>&lt;34.4</td>
<td>76/83</td>
</tr>
<tr>
<td>Peak VO2</td>
<td>0.76*</td>
<td>0.68–0.84</td>
<td>&gt;14.2</td>
<td>62/79</td>
</tr>
<tr>
<td>Change in PETCO2 from rest to VT</td>
<td>0.72*</td>
<td>0.63–0.81</td>
<td>&gt;1.8</td>
<td>81/61</td>
</tr>
<tr>
<td>PETCO2 at VT</td>
<td>0.82*</td>
<td>0.75–0.89</td>
<td>&gt;36.1</td>
<td>77/69</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.61**</td>
<td>0.51–0.71</td>
<td>&gt;22.3</td>
<td>65/56</td>
</tr>
</tbody>
</table>

* p<0.001.
** p<0.05.

< and > indicate better prognosis.
ROC curve analysis revealed that the VE/VCO2 slope [chi-square: 44.7, hazard ratio 1.08 (95% CI: 1.06–1.11), p<0.001], peak VO2 [chi-square: 27.9, hazard ratio 0.85 (95% CI: 0.79–0.91), p<0.001], PETCO2 at VT [chi-square: 40.5, hazard ratio 0.86 (95% CI: 0.82–0.90), p<0.001], peak PETCO2 [chi-square: 38.1, hazard ratio 0.87 (95% CI: 0.83–0.91), p<0.001], change in PETCO2 from rest to VT [chi-square: 14.7, hazard ratio 0.86 (95% CI: 0.80–0.93), p<0.001] and LVEF [chi-square: 4.7, hazard ratio 0.98 (95% CI: 0.95–1.0), p<0.05] were all prognostically significant. Using the threshold values determined by ROC curve analysis for continuous variables, Table 5 lists the chi-square and hazard ratios for the resting and CPX variables expressed categorically. All resting and CPX variables were significant univariate predictors of cardiac-related events when expressed categorically. Four groups defined by the VE/VCO2 slope, peak VO2 and PETCO2 at VT threshold values.

Again using categorical expressions for resting and CPX variables, multivariate Cox regression analysis results are listed in Table 6. PETCO2 at the VT, rather than change in PETCO2 or PETCO2 at peak exercise, was included in the multivariate regression given its higher area under the ROC curve and hazard ratio. The VE/VCO2 slope was the strongest predictor of 1-year cardiac-related events. Peak VO2 and PETCO2 at the VT added significant predictive value and were retained in the regression. LVEF, NYHA class and HF etiology did not add additional predictive value and were removed from the regression. The Cox-proportional hazard assumption was met for all variables.

Kaplan–Meier analysis results are illustrated in Fig. 1. Event-free survival characteristics were distinct among the four groups defined by the VE/VCO2 slope, peak VO2 and PETCO2 at VT threshold values.

9. Discussion

The results of the present study indicate that PETCO2 obtained during CPX has prognostic value in patients with HF. Specifically, the change in PETCO2 from rest to the VT, PETCO2 at the VT and PETCO2 at peak exercise were all significant predictors of outcome. These findings extend the diagnostic analyses performed by Matsumoto et al. [9] and Tanabe et al. [10], who both demonstrated changes in PETCO2 during CPX were significantly related to cardiac output and HF severity. In addition, Matsumoto et al. [9] concluded that decreased CO2 production, abnormal ventilatory patterns (rapid and shallow breathing) and compensatory hyperventilation did not appear to explain the lower
univariate predictors of cardiac-related events, ROC curve analysis revealed that PETCO2 at the VT was the strongest predictor of risk. The change in PETCO2 from rest to VT was a reflection of increased pulmonary perfusion and therefore cardiac output with exercise. While the change in PETCO2 from rest to VT was prognostically significant, it did not appear to be as powerful as the absolute value obtained at the VT. In other words, individuals with a large increase in PETCO2 during the initial stages of exercise, but still having an abnormally low PETCO2 value at VT, are likely to have compromised cardiac function and therefore a poor prognosis. Additionally, a decrease in PETCO2 beyond the VT would be expected as lactate accumulation stimulates a further increase in ventilation. The reduction in PETCO2 from VT to peak is therefore not necessarily reflective of declining cardiac output. The prognostic significance of PETCO2 at peak exercise is likely a reflection of it being lower throughout the exercise test (lower PETCO2 at VT = lower PETCO2 at peak). The additional influence of increased ventilation on PETCO2 at peak exercise, a response which varies widely between individuals, has a potentially negative impact on its prognostic power. The ability of PETCO2 at the VT to more purely reflect cardiac output, without the influence of increased ventilation, may help to explain the differences in prognostic strength between the submaximal and maximal expressions of PETCO2. Regardless of the underlying mechanism, PETCO2 at the VT appears to provide optimal prognostic information in comparison to other expressions.

The use of CPX in the HF population for diagnostic/prognostic purposes has been accepted in clinical practice for several years [20]. The clinical application of data obtained from CPX, however, has been primarily limited to peak VO2. In recent years, a number of additional CPX variables have demonstrated prognostic value in the HF population. In particular, the VE/VCO2 slope has been shown to be a superior prognostic variable compared to peak VO2 in several previous investigations [5,7,21,22]. The results of the present study confirm the prognostic power of the VE/VCO2 slope among variables obtained from CPX in patients with HF. In our multivariate regression analysis, both peak VO2 and PETCO2 at VT added prognostic value to the VE/VCO2 slope. The Kaplan–Meier analysis illustrated in Fig. 1 demonstrates the value of combining these three CPX variables for prognostic assessment. Clinical practice guidelines for patients with HF should consider endorsing the assessment of exercise variables beyond peak VO2 that have demonstrated prognostic value.

Our group has recently assessed the impact of time past CPX on the prognostic value of peak VO2 and the VE/VCO2 slope [23]. We found the decline in specificity was much larger than the increase in sensitivity for predicting risk as time past CPX lengthened. From these findings, we suggested that CPX data are best applied for a limited period of time, with a 1-year period possibly striking an acceptable balance between sensitivity and specificity. For this reason, we chose to limit the tracking period to 1 year in the present investigation as there is no reason to suspect the prognostic strength of PETCO2 would be any different as the time following CPX increased.

Although a large number of cardiac events were recorded during the tracking period, the relatively small sample size of the present study is a limitation. The fact that none of the subjects were NYHA class IV may also limit application of our findings to groups with more severe HF. Furthermore, we did not include a direct assessment of cardiac output during exercise. While we are confident that lower PETCO2 values during exercise were a consequence of decreased cardiac output, the lack of direct measurements is a limitation. Lastly, a number of previous investigations have recently examined the impact of beta-blockade on the prognostic characteristics of CPX variables, primarily peak VO2 [24–27]. These studies have generally found that peak VO2 is still predictive of outcomes in patients receiving a beta-blocking agent. Forty-three percent of the subjects in the present study were prescribed a beta-blocker. Again, the small overall sample size of the present study limited the ability to examine the influence of beta-blockade on the prognostic value of PETCO2. Given the previously demonstrated link between cardiac output and PETCO2 [9,10], there is no reason to suspect use of a beta-blocking agent would attenuate its prognostic value. Future research should investigate the impact of beta-blocker therapy on the prognostic value of PETCO2 as well as other CPX variables.

In conclusion, previous studies have reported a strong relationship between PETCO2 and cardiac output in patients with HF, demonstrating this CPX variable has diagnostic value [9,10]. The present study is to our knowledge the first to demonstrate that PETCO2, particularly at the VT, also has prognostic value. Importantly, this response appears to add predictive value to more established CPX variables. Future research should be directed toward developing multivariable CPX prognostic algorithms, allowing for more accurate prognostic assessments in the HF population.

References


