Prognostic value of resting end-tidal carbon dioxide in patients with heart failure

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Abstract

Background: Cardiopulmonary exercise testing (CPET) variables provide valuable prognostic information in the heart failure (HF) population. The purpose of the present study is to assess the ability of resting end-tidal carbon dioxide partial pressure (PETCO2) to predict cardiac-related events in patients with HF.

Methods: 121 subjects diagnosed with compensated HF underwent CPET on an outpatient basis. Mean age and ejection fraction were 49.3 years (± 14.7) and 28.4% (±13.4), respectively. Resting PETCO2 was determined immediately prior to the exercise test in the seated position. Peak oxygen consumption (VO2) and the minute ventilation-carbon dioxide production (VE/VCO2) slope were also acquired during CPET.

Results: There were 41 cardiac-related hospitalizations and 9 cardiac-related deaths in the year following CPET. Mean resting PETCO2, peak VO2 and VE/VCO2 slope were 34.1 mmHg (±4.6), 14.5 ml·kg⁻¹·min⁻¹ (±5.1) and 35.9 (±8.7) respectively. Univariate Cox regression analysis revealed that resting PETCO2 (Chi-square = 28.4, \( p < 0.001 \)), peak VO2 (Chi-square = 21.6, \( p < 0.001 \)) and VE/VCO2 slope (Chi-square = 54.9, \( p < 0.001 \)) were all significant predictors of cardiac related events. Multivariate Cox regression analysis revealed resting PETCO2 added to the prognostic value of VE/VCO2 slope in predicting cardiac related events (residual Chi-square = 4.4, \( p = 0.04 \)). Peak VO2 did not add additional value and was removed (residual Chi-square = 3.2, \( p = 0.08 \)).

Conclusions: These results indicate a resting ventilatory expired gas variable possesses prognostic value independently and in combination with an established prognostic marker from the CPET. Resting PETCO2 may therefore be a valuable objective measure to obtain during both non-exercise and exercise evaluations in patients with HF.

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1. Background

Several ventilatory expired gas variables obtained during exercise in addition to peak VO2 have recently been demonstrated to have prognostic value in patients with heart failure (HF) [1–3]. In fact, although peak VO2 is the most frequently assessed cardiopulmonary exercise response in clinical practice [2,4,5], more recently derived ventilatory expired gas variables, including oxygen uptake on-kinetics and the minute ventilation-carbon dioxide production relationship (VE/VCO2 slope), may be prognostically superior to peak VO2 [2,6]. These responses have been promoted because they can be obtained submaximally, which has obvious patient comfort and safety advantages. Clearly, further research directed toward optimizing prognostic data extracted from ventilatory expired gas analysis in the HF population is warranted.

In this context, most of the research examining prognosis in HF has been directed toward ventilatory expired gas measures obtained during cardiopulmonary exercise testing (CPET). A prognostic assessment of any resting ventilatory expired gas variable has, to our knowledge, not been
conducted. The resting partial pressure of end-tidal carbon dioxide ($P_{ETCO_2}$) may have prognostic value in patients with HF. Previous research has already demonstrated a significant relationship between $P_{ETCO_2}$ during exercise and cardiac function in patients with HF [7,8]. Numerous investigations have further demonstrated a positive relationship between resting $P_{ETCO_2}$ and cardiac output [9–14]. None of these latter studies involved HF patients per se and data collection was largely conducted during intubation and sedation. Translation of these results to an ambulatory HF population is plausible, since a low cardiac output equates to a low resting $P_{ETCO_2}$. In making this assumption, one can reasonably hypothesize a lower resting $P_{ETCO_2}$ value in patients with HF would indicate poorer cardiac function and therefore poorer prognosis. The purpose of the present study was to therefore assess the ability of resting $P_{ETCO_2}$, independently and in combination with peak VO$_2$, VE/VCO$_2$ slope and several other clinically relevant variables, to predict cardiac-related events in a group of patients diagnosed with HF.

2. Materials and methods

One hundred and twenty-one consecutive subjects diagnosed with compensated HF underwent a symptom-limited CPET between 5/15/97 and 10/18/04 at Virginia Commonwealth University Medical Center and retrospectively assessed for this study. 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 CPET procedures were, however, identical for all subjects. 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 six 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.

2.1. 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 three-liter syringe.

2.2. Testing procedure and data collection

Resting $P_{ETCO_2}$ was collected immediately prior to exercise testing. Subjects were in the sitting position and ventilating through the mouthpiece for at least 30 s before collection of resting $P_{ETCO_2}$ data began. Data collection was not initiated until the individuals conducting the exercise test observed a relaxed ventilatory pattern. Previous work by our group has demonstrated resting $P_{ETCO_2}$ is highly reliable thereby supporting the use of a single data collection session in the present investigation (intraclass correlation coefficient=0.93, standard error of measurement with 95% confidence limits: ±2.1 mmHg) [15].

Symptom-limited CPET was conducted using a treadmill. The modified ramping protocol selected for testing consisted of approximately 2 mlO$_2$·kg$^{-1}$·min$^{-1}$ increases in workload every 30 s [5,16,17]. 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. The same conservative 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.

2.3. Data analysis

Resting $P_{ETCO_2}$ was defined as the two-minute averaged value prior to exercise testing in the seated position. Oxygen consumption (ml·kg$^{-1}$·min$^{-1}$), CO$_2$ (L/min), and VE (L/min) were collected throughout the exercise test. Peak VO$_2$ was expressed as the highest 10-s average value obtained during the last 30-s stage of the exercise test. The ventilatory equivalents method was used to determine oxygen consumption at ventilatory threshold (VT) [18]. Resting and peak oxygen pulse was determined by dividing the ten second averaged value of oxygen uptake (ml/min) by the ten second averaged value of heart rate at peak exercise. The ventilatory dead space to tidal volume ratio (VD/VT) was also estimated at rest and maximal exercise. Ten second averaged VE and CO$_2$ data, from the initiation of exercise to peak, were input into spreadsheet software (Microsoft Excel, Microsoft Corp., Bellevue, WA) to calculate the VE/VCO$_2$ slope via least squares linear regression ($y=mx+b$, $m=$slope). Previous work by our group has shown this calculation method of VE/VCO$_2$ slope to be prognostically optimal [19].
2.4. Endpoints

Subjects were followed for cardiac-related mortality and hospitalization for one-year following exercise testing 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. All subjects were followed as outpatients by Virginia Commonwealth University Medical Center. The subjects requiring hospitalization were most frequently received their care at Virginia Commonwealth University Medical Center. In the rare event subjects were hospitalized at another institution for emergent care, a discharge note was sent to Virginia Commonwealth University Medical Center and maintained in the patients chart. We are highly confident all events were captured for this sample.

2.5. Statistical analysis

The mean and standard deviation were reported for key variables. Pearson product moment correlation was used to assess the relationship between resting PETCO2 and key baseline and exercise variables. Univariate Cox regression analysis was used to determine the ability of body mass index (BMI), left ventricular ejection fraction (LVEF), beta-blockade use, New York Heart Association (NYHA) Class, resting PETCO2, peak VO2 and VE/VCO2 slope to predict cardiac-related events over the one-year tracking period. Multivariate Cox regression analysis (forward stepwise method) was used to assess the combined ability of the variables found to be prognostically significant in the univariate analysis (NYHA Class, resting PETCO2, peak VO2 and VE/VCO2 slope) to also predict one year cardiac-related events. Entry and removal p-values were set at 0.05 and 0.10 respectively. Receiver operating characteristic (ROC) curve analysis assessed the classification scheme and determined the optimal threshold value of ventilatory expired gas variables retained in the multivariate Cox regression analysis. Univariate Cox regression analysis was again used to determine the hazard ratio of optimal threshold values as determined by ROC curve analysis. Kaplan–Meier analysis examined event-free survival characteristics of subjects based on the combined optimal threshold values of resting PETCO2 and VE/VCO2 slope, independently. Kaplan–Meier analysis was also used to assess the event-free survival characteristics of subjects based on the combined optimal threshold values of resting PETCO2 and VE/VCO2 slope. A statistical software program was used for all data analysis (SPSS 12.0 for Windows, Chicago, IL). All statistical tests with a p-value < 0.05 were considered significant.

3. Results

None of the CPETs were terminated prematurely secondary to signs/symptoms of ischemia, arrhythmias or

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting PETCO2 (mmHg)</td>
<td>34.1 ± 4.6</td>
</tr>
<tr>
<td>Peak VO2 (ml·kg⁻¹·min⁻¹)</td>
<td>14.5 ± 5.1</td>
</tr>
<tr>
<td>VO2 at VT (ml·kg⁻¹·min⁻¹)</td>
<td>11.6 ± 3.9</td>
</tr>
<tr>
<td>VE/VCO2 Slope</td>
<td>35.9 ± 8.7</td>
</tr>
<tr>
<td>Peak RER</td>
<td>1.05 ± 0.1</td>
</tr>
<tr>
<td>Resting oxygen pulse (ml/beat)</td>
<td>4.0 ± 1.5</td>
</tr>
<tr>
<td>Peak oxygen pulse (ml/beat)</td>
<td>10.1 ± 4.0</td>
</tr>
<tr>
<td>Resting VD/VT</td>
<td>0.37 ± 0.07</td>
</tr>
<tr>
<td>Peak VD/VT</td>
<td>0.25 ± 0.07</td>
</tr>
</tbody>
</table>

resting PETCO2, peak VO2 and VE/VCO2 slope to predict cardiac-related events over the one-year tracking period.

Table 1

Subject characteristics

<table>
<thead>
<tr>
<th>Number of subjects</th>
<th>121 (76 male/45 female)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>49.3 ± 14.7</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>28.7 ± 6.8</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>28.4% ± 13.4</td>
</tr>
<tr>
<td>New York Heart Association Class (number of subjects)</td>
<td></td>
</tr>
<tr>
<td>Class I</td>
<td>22</td>
</tr>
<tr>
<td>Class II</td>
<td>35</td>
</tr>
<tr>
<td>Class III</td>
<td>64</td>
</tr>
<tr>
<td>Heart failure etiology (ischemic/non-ischemic)</td>
<td>51/70</td>
</tr>
<tr>
<td>ACE inhibitor (number of subjects)</td>
<td>92</td>
</tr>
<tr>
<td>Cardiac glycoside (number of subjects)</td>
<td>90</td>
</tr>
<tr>
<td>Diuretic (number of subjects)</td>
<td>100</td>
</tr>
<tr>
<td>Nitrate (number of subjects)</td>
<td>29</td>
</tr>
<tr>
<td>Beta-blocker (number of subjects)</td>
<td>59</td>
</tr>
</tbody>
</table>

*: Determined by two-dimensional echocardiography.

Table 2

Key ventilatory expired gas variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting PETCO2 (mmHg)</td>
<td>34.1 ± 4.6</td>
</tr>
<tr>
<td>Peak VO2 (ml·kg⁻¹·min⁻¹)</td>
<td>14.5 ± 5.1</td>
</tr>
<tr>
<td>VO2 at VT (ml·kg⁻¹·min⁻¹)</td>
<td>11.6 ± 3.9</td>
</tr>
<tr>
<td>VE/VCO2 Slope</td>
<td>35.9 ± 8.7</td>
</tr>
<tr>
<td>Peak RER</td>
<td>1.05 ± 0.1</td>
</tr>
<tr>
<td>Resting oxygen pulse (ml/beat)</td>
<td>4.0 ± 1.5</td>
</tr>
<tr>
<td>Peak oxygen pulse (ml/beat)</td>
<td>10.1 ± 4.0</td>
</tr>
<tr>
<td>Resting VD/VT</td>
<td>0.37 ± 0.07</td>
</tr>
<tr>
<td>Peak VD/VT</td>
<td>0.25 ± 0.07</td>
</tr>
</tbody>
</table>

*: p < 0.001.

Table 3

Pearson product moment correlation between resting PETCO2 and key variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Resting PETCO2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>−0.10</td>
</tr>
<tr>
<td>Left ventricular ejection fraction</td>
<td>0.13</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.34*</td>
</tr>
<tr>
<td>VE/VCO2 slope</td>
<td>−0.62*</td>
</tr>
<tr>
<td>Peak VO2</td>
<td>0.32*</td>
</tr>
<tr>
<td>Resting oxygen pulse</td>
<td>0.39*</td>
</tr>
<tr>
<td>Peak oxygen pulse</td>
<td>0.36*</td>
</tr>
<tr>
<td>Resting VD/VT</td>
<td>−0.30*</td>
</tr>
<tr>
<td>Peak VD/VT</td>
<td>−0.35*</td>
</tr>
</tbody>
</table>

*p < 0.001.
hemodynamic abnormalities (excessive hypo/hypertension). There were 41 cardiac-related hospitalizations and 9 cardiac-related deaths in the year following CPET. Heart rate at rest and maximal exercise were 80.4 (±16.0) and 124.4 (±25.2) beats per minute respectively. Key ventilatory expired gas variables are listed in Table 2.

Based on individual peak VO$_2$ values, Weber classification for the group was as follows; Weber class A: 17, Weber class B: 25, Weber class C: 57, Weber class D: 22. Sixty-six percent of the subjects in the present study achieved a peak RER $\geq 1.0$. Pearson product correlation results are listed in Table 3. Resting PETCO$_2$ was not significantly correlated with age or LVEF. The relationship between resting PETCO$_2$ and peak VO$_2$, VE/VCO$_2$ slope, oxygen pulse, VD/VT, and BMI were statistically significant.

Univariate and Multivariate Cox regression analysis results are listed in Table 4. Univariate Cox regression analysis revealed NYHA class, resting PETCO$_2$, peak VO$_2$ and VE/VCO$_2$ slope were all significant predictors of cardiac-related events. Body mass index, LVEF and beta-blockade use were not significant predictors of outcome in the univariate Cox regression analysis. Multivariate Cox regression analysis revealed NYHA class and resting PETCO$_2$ added to the prognostic value to VE/VCO$_2$ slope in predicting one year cardiac-related events. Peak VO$_2$ did not add additional value and was removed from the multivariate regression.

Receiver operating characteristic curves for resting PETCO$_2$ and VE/VCO$_2$ slope as continuous variables are illustrated in Figs. 1 and 2, respectively.

Optimal threshold values for resting PETCO$_2$ (greater value preferred) and VE/VCO$_2$ slope (lesser value preferred) were $\leq 33.0$ mmHg (ROC area=0.74, $p<0.001$, sensitivity =75%, Specificity =72%) and $\geq 34.4$ (ROC area=0.84, $p<0.001$, sensitivity =78%, Specificity =82%), respectively. Univariate hazard ratios for resting PETCO$_2$ and VE/VCO$_2$ slope threshold values are listed in Table 5.

Kaplan Meier analyses using the predetermined threshold values of resting PETCO$_2$ alone, VE/VCO$_2$ slope alone and resting PETCO$_2$ combined with VE/VCO$_2$ slope are illustrated in Figs. 3–5.

Using the optimal resting PETCO$_2$ threshold value as determined by ROC curve analysis, sixty-seven subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Area under the curve</th>
<th>95% Confidence interval</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting PETCO$_2$</td>
<td>0.74</td>
<td>0.63–0.84</td>
<td>$&lt;0.001$</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>End point</th>
<th>Threshold criteria</th>
<th>Hazard ratio</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac-related Events (1 yr)</td>
<td>Resting PETCO$_2$ $\leq 33.0$ = negative prognosis</td>
<td>4.8</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>Cardiac-related Events (1 yr)</td>
<td>VE/VCO$_2$ slope $\geq 34.4$ = negative prognosis</td>
<td>7.2</td>
<td>$&lt;0.0001$</td>
</tr>
</tbody>
</table>
demonstrated a favorable resting PETCO2 value while the remaining fifty-four possessed an unfavorable value. The percentage of subjects who were event-free for the one-year tracking period with a favorable value and unfavorable resting PETCO2 value was 79.1% and 33.3% respectively.

Using the optimal VE/VCO2 slope threshold value as determined by ROC curve analysis, sixty-two subjects demonstrated a favorable VE/VCO2 slope value while the remaining fifty-nine possessed an unfavorable value. The percentage of subjects who were event-free for the one-year tracking period with a favorable value and unfavorable VE/VCO2 slope value was 85.5% and 30.5% respectively.

When combining resting PETCO2 with VE/VCO2 slope, forty-eight subjects demonstrated favorable values for both variables, thirty-three subjects demonstrated one unfavorable value (resting PETCO2 or VE/VCO2 slope) and forty subjects demonstrated unfavorable values for both variables. The number of subjects who were event-free for the one-year tracking period with no unfavorable values, one unfavorable value and two unfavorable values were 91.7.1%, 54.5% and 22.2% respectively.

### 4. Discussion

The results of the present study indicate that resting PETCO2 is significantly correlated with CPET variables previously shown to have diagnostic and/or prognostic value in HF. There does not appear to be a clinically significant relationship between resting PETCO2 and either age or LVEF. A significant positive correlation between resting PETCO2 and BMI was, however, apparent. This relationship indicates individuals with a higher BMI tended to have a more favorable resting PETCO2 value. This latter
finding is consistent with previous investigations reporting
improved prognosis with increased BMI in patients with
HF [20]. More importantly from a clinical perspective, 
resting $P_{ET}CO_2$ appears to be a significant predictor of
cardiac-related events both independently and in combina-
tion with an established clinical (NYHA class) and
ventilatory expired gas (VE/VCO₂ slope) variable. Acquis-
tion of resting $P_{ET}CO_2$ may therefore be warranted during
both resting and exercise clinical evaluations in patients
with HF.

A significant relationship between resting $P_{ET}CO_2$ and
cardiac output has been demonstrated in a number of
previous investigations in subjects not diagnosed with HF.
In a group of patients undergoing abdominal aortic
aneurysm repair, Shibutani et al. [21] found $P_{ET}CO_2$ was
significantly correlated with changes in cardiac output
during surgery ($R^2 = 0.82$, $p < 0.01$). Wahba et al. [14] found
$P_{ET}CO_2$, taken before and after elective open-heart surgery,
was strongly related to changes in cardiac index ($r = 0.75$,
$p < 0.001$). In an intubated/sedated model, findings from
I’dris et al. [11] suggested $P_{ET}CO_2$ was able to accurately
reflect cardiac output over a wide range of flow rates,
including very low flow rates. In 23 subjects who were in
cardiac arrest, Garnett et al. [22] reported an immediate and
significant increase in $P_{ET}CO_2$ in the 10 subjects who
experienced a return in spontaneous circulation. Lastly,
Asplin et al. [23] found that higher initial $P_{ET}CO_2$ values
predicted the return of spontaneous circulation in 27 patients
suffering cardiac arrest. These previous investigations
provided our impetus to hypothesize that resting $P_{ET}CO_2$
would be a significant predictor of cardiac-related events in
patients with HF secondary to it’s reflection of cardiac
function. In the present study, a significant positive
correlation between resting $P_{ET}CO_2$ and oxygen pulse at
rest and peak exercise, a non-invasive indicator or cardiac
function, was found. A significant negative correlation
between resting $P_{ET}CO_2$ and VD/VT at rest and peak
exercise, a non-invasive indicator of ventilation–perfusion
matching, was also found. This latter finding may also be
attributed to the link between cardiac function and
pulmonary perfusion. Previous research has already dem-
strated a significant relationship between $P_{ET}CO_2$ during
exercise and cardiac function in subjects with HF [7,8]. The
results of the present study provide initial evidence that
there is also a relationship between $P_{ET}CO_2$ and cardiac
function at rest in subjects with HF. Additional research is,
however, required to more thoroughly examine the associ-
atation between resting $P_{ET}CO_2$ and cardiac function in the
HF population.

Patients diagnosed with HF frequently attend outpatient
clinics at regular intervals to assess the stability of their
condition and alter medical management as indicated. A
number of resting measures, including NYHA class,
ecocardiography [3,24–26], ECG [26–30], blood pres-
sure [31–33] and inflammatory [34–37] and neurohormo-
nal blood markers, [38,39] have been shown to provide
information pertinent to prognosis and disease severity and
are therefore frequently ascertained during clinical visits.
The current results suggest consideration should be given
to adding resting $P_{ET}CO_2$ to the list of measures
incorporated into the non-exercise assessment of HF. The
non-invasive nature by which resting $P_{ET}CO_2$ can be
rapidly assessed makes this a promising clinical measure,
particularly in rural medical settings where assessment
techniques may be limited. Future research should be
directed toward comparing the prognostic power of resting
$P_{ET}CO_2$ to a more comprehensive list of clinically
established resting measures.

Cardiopulmonary exercise testing is considered a stand-
ard of care in the HF population and is therefore frequently
employed to assess HF severity and assist in determining
appropriateness for transplant candidacy.[40,41] Although
the focus of CPET in HF has been on peak VO₂, a number
of recent investigations have challenged its prognostic
power relative to other CPET variables, particularly the
VE/VCO₂ slope [3–6,42–44]. The results of the present
study are consistent with these recent investigations in that
the VE/VCO₂ slope had greater prognostic power than peak
VO₂. Peak VO₂ has two potential limitations when
assessing prognosis. First, a true assessment of peak VO₂
is dependent on subject effort. Even with the most diligent
efforts by clinicians to illicit maximal effort, a percentage of
HF patients will voluntarily terminate the exercise test
prematurely. This was readily apparent in the present study
as 34% of our subjects failed to attain a peak RER $\geq 1.0$. A
second potential limitation is the contribution peripheral
metabolism has on peak VO₂. This contribution is made
apparent by investigations demonstrating that high values
for peak VO₂ are paralleled by superior skeletal muscle
metabolic capacity [45]. Although studies citing superior
peripheral metabolic function attribute this phenomenon to
exercise training, one should not expect those patients with
HF who are similarly sedentary or trained to have
homogeneous muscle fiber characteristics [46]. Thus, two
HF patients with similar cardiac but differing skeletal
muscle function, who both put forth a maximal effort
during exercise, may have different values for peak VO₂.
This issue was raised by the work of Wilson et al. [47] who
reported that among 64 patients evaluated for heart trans-
plantation, cardiac output and pulmonary wedge pressure
responses to exercise differed markedly despite patients
having similar values for peak VO₂. These results addition-
ally indicate that resting $P_{ET}CO_2$ may add prognostic value
when assessed in combination with the VE/VCO₂ slope in
estimating risk in HF, a finding that has not been previously
reported. Both resting $P_{ET}CO_2$ and the VE/VCO₂ slope
are not influenced by subject effort, which may be a primary
reason for their superior prognostic value compared to peak
VO₂. As this type of evidence continues to mount,
consideration should be given to revising established
guidelines, which presently recommend only the assessment
of peak VO₂ for risk stratification in HF [40,41]. Specifi-
cally, the VE/VCO₂ slope appears to be the superior prognostic CPET variable. If future research supports our findings, the inclusion of resting PₚETCO₂ when applying CPET results in HF may also be warranted.

Individuals with HF can shift from a stable to an uncompensated status (or vice versa) rather abruptly. Limiting the post-CPET tracking period to one-year may be clinically optimal given the fluid nature of cardiac function in the HF patient. We recently completed an analysis of the impact of time past CPET on the prognostic characteristics of VE/VCO₂ slope and peak VO₂ in subjects with HF [48]. This analysis indicated prognostic sensitivity modestly rose while specificity dramatically fell for both CPET variables greater than one-year post exercise testing. A one-year tracking period may therefore strike a sufficient balance between avoiding outdated information and the economic constraints of multiple exercise tests.

Additionally, most research examining the prognostic value of CPET data do not use hospitalization as an endpoint. Given that HF is the primary hospital diagnostic related group among Medicare patients [49], analysis of measures predicting hospitalization in this population seems warranted. The ability of the VE/VCO₂ slope and resting PₚETCO₂ to effectively predict hospitalization may help identify high-risk patients and provide appropriate interventions on an outpatient basis thereby preventing nonfatal adverse events (hospitalization) and reduce health care costs.

The relatively small sample size in the present investigation must be considered a limitation. Furthermore, a number of subjects in the present study were not prescribed a beta-blocking agent at the time of CPET. Several recent investigations have demonstrated peak VO₂ remains prognostically significant in patients with CHF receiving a beta-blocking agent [50,51]. The prognostic impact of beta-blockade use on other CPET variables, however, has not been investigated thoroughly. Additional research assessing the association between resting PₚETCO₂, cardiac function and outcomes, as well as the impact of beta-blockade use, is needed before a universal recommendation for including resting PₚETCO₂ in the clinical assessment of patients with HF can be made.

5. Conclusions

In conclusion, ventilatory expired gas analysis during exercise continues to demonstrate clinical value in patients with HF. Variables ascertained from this analysis have traditionally been collected during exercise testing. The results of the present study indicate the value of ventilatory expired gas analysis may extend past that which is gained during physical exertion. Efforts should be directed toward maximizing the information gained from this non-invasive assessment technique and promoting the implementation of recent research findings into clinical practice.

References


