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Prognostic value of end-tidal carbon dioxide during exercise testing in heart failure

Ross Arena [a,*], Marco Guazzi [b], Jonathan Myers [c]

[a] Department of Physical Therapy, Box 980224, Virginia Commonwealth University, Health Sciences Campus, Richmond, Virginia, 23298-0224, United States
[b] University of Milano, San Paolo Hospital, Cardiopulmonary Laboratory, Cardiology Division, University of Milano, San Paolo Hospital, Milano, Italy
[c] VA Palo Alto Health Care System, Cardiology Division, Stanford University, Palo Alto, CA

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Abstract

Background: The partial pressure of end-tidal carbon dioxide production ($P_{ET}CO_2$) 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 $P_{ET}CO_2$ 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 (VO_2), the minute ventilation–carbon dioxide production (VE/VCO_2) slope and $P_{ET}CO_2$ were determined.
Results: Receiver operating characteristic (ROC) curve analysis revealed that $P_{ET}CO_2$ at the ventilatory threshold (VT) was a significant predictor of cardiac-related events (ROC area = 0.82, $p < 0.001$). The optimal $P_{ET}CO_2$ 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, $P_{ET}CO_2$ at VT added significant predictive value to the VE/VCO_2 slope and peak VO_2.
Conclusion: These results indicate that $P_{ET}CO_2$ 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.

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 (VO_2) 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 (VCO_2), 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 ($P_{ET}CO_2$) is one such CPX variable that may possess prognostic value in the HF population. Matsumoto et al. [9] found that $P_{ET}CO_2$ 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 $P_{ET}CO_2$ (<38.5 mm Hg) to predict a lower cardiac output during exercise (cardiac index < 5.11 l/min/m^2 at peak exercise) were 76.5% and 75.0%, respectively. Tanabe et al. [10] likewise reported a significant correlation between $P_{ET}CO_2$ and cardiac index at peak exercise in subjects diagnosed with HF. The results from these investigations indicate that $P_{ET}CO_2$ closely reflects the cardiac output response to exercise and therefore may have diagnostic applications in patients with HF.

* Corresponding author. Tel.: +1 804 828 0234 (office); fax: +1 804 828 8111.
E-mail address: raarena@vcu.edu (R. Arena).

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Table 1
Subject characteristics

Number of subjects	130 (77 male/53 female)
Age (years)	49.2±14.5 [a]
Left ventricular ejection fraction (%) [b]	28.5±13.1 [a]
Resting $P_{ET}CO_2$ (mm Hg)	34.1±4.6 [a]
New York Heart Association Class (I/II/III)	27/52/51
Heart failure etiology (ischemic/non-ischemic)	54/76
ACE inhibitor (number of subjects)	99
Cardiac glycoside (number of subjects)	96
Diuretic (number of subjects)	108
Nitrate (number of subjects)	31
Beta-blocker (number of subjects)	59

[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 O_2 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 VO_2, 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, $\geq$2 mm of horizontal or downsloping ST segment depression or a drop in systolic blood pressure $\geq$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}), VCO_2 (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 VO_2 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 VCO_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 [18] and others [19] have shown this method of calculating the VE/VCO_2 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 $P_{ET}CO_2$ and age, LVEF, peak VO_2 and the VE/CO_2 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 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 [− 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.

Table 2
Mean CPX values

	Mean	Standard deviation
Peak VO_2 (ml O_2 kg^{-1} min^{-1})	14.5	±5.2
Peak RER	1.05	±0.11
VE/VCO_2 slope	36.4	±9.3
$P_{ET}CO_2$ at VT (mm Hg)	37.3	±5.9
Change in $P_{ET}CO_2$ from rest to VT (mm Hg)	3.1	±3.6
$P_{ET}CO_2$ at peak (mm Hg)	34.1	±6.4

Table 3
Pearson product moment correlation analysis

	Age	LVEF	VE/CO_2 slope	Peak VO_2
$P_{ET}CO_2$ at VT	−0.18 *	0.15	−0.78 **	0.50 **
Change in $P_{ET}CO_2$ from rest to VT	−0.14	0.15	−0.50 **	0.38 **
$P_{ET}CO_2$ at peak	−0.12	0.11	−0.88 **	0.52 **

* $p<0.05$.
** $p<0.01$.

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.

Pearson product moment correlation results are listed in Table 3. $P_{ET}CO_2$ was significantly correlated with peak VO_2 and the VE/VCO_2 slope. $P_{ET}CO_2$ at the VT was weakly correlated with age. None of the other $P_{ET}CO_2$ variables were correlated with age or LVEF.

There were eight cardiac-related deaths and 44 cardiac-related hospitalizations during the 1-year tracking period. There were an additional eight cardiac-related deaths in subjects who were hospitalized for a cardiac-related condition at an earlier point (weeks to months). None of the subjects died from non-cardiac causes during the tracking period. All subjects admitted to the hospital had either a primary or secondary discharge diagnosis of HF. None of the hospital admissions were the result of an elective procedure.

Table 4
ROC curve analysis

	ROC area	95% CI	Optimal threshold [a]	Sensitivity/ specificity
VE/VCO_2 slope	0.83 *	0.75–0.90	<34.4	76/83
Peak VO_2	0.76 *	0.68–0.84	>14.2 (ml O_2 kg^{-1} min^{-1})	62/79
$P_{ET}CO_2$ at VT	0.82 *	0.75–0.89	>36.1 (mm Hg)	77/69
Change in $P_{ET}CO_2$ from rest to VT	0.72 *	0.63–0.81	>1.8 (mm Hg)	81/61
$P_{ET}CO_2$ at peak	0.80 *	0.72–0.87	>33.3 (mm Hg)	73/69
LVEF	0.61 **	0.51–0.71	>22.3	65/56

[a] < and > indicate better prognosis.
* $p<0.001$.
** $p<0.05$.

Table 5
Univariate Cox regression analysis

	Optimal threshold[a]	Chi-square	Hazard ratio	95% CI
VE/VCO_2 slope	<34.4	39.5 *	7.2 *	3.5–14.9
Peak VO_2	>14.2 (ml O_2 kg^{-1} min^{-1})	18.9 *	3.9 *	2.0–7.6
$P_{ET}CO_2$ at VT	>36.1 (mm Hg)	30.8 *	4.6 *	2.6–8.4
Change in $P_{ET}CO_2$ from rest to VT	>1.8 (mm Hg)	28.2 *	4.1 *	2.3–7.3
$P_{ET}CO_2$ at peak	>33.3 (mm Hg)	24.5 *	4.0 *	2.2–7.2
LVEF	>22.3 (%)	6.7 **	2.0 **	1.2–3.5
NYHA	I/II/III	23.5 *	2.8 *	1.8–4.4
HF etiology	Ischemic vs. non-ischemic[b]	7.4 **	2.1 **	1.2–3.6

[a] < and > indicate better prognosis.
[b] Ischemic etiology = worse prognosis.
* $p<0.001$.
** $p<0.05$.

ROC curve analysis revealed all CPX variables and LVEF were significant predictors of cardiac events. Results from the ROC curve analysis are listed in Table 4.

As continuous variables, univariate Cox regression analysis revealed that the VE/VCO_2 slope [chi-square: 44.7, hazard ratio 1.08 (95% CI: 1.06–1.11), $p<0.001$], peak VO_2 [chi-square: 27.9, hazard ratio 0.85 (95% CI: 0.79–0.91), $p<0.001$], $P_{ET}CO_2$ at VT [chi-square: 40.5, hazard ratio 0.86 (95% CI: 0.82–0.90), $p<0.001$], peak $P_{ET}CO_2$ [chi-square: 38.1, hazard ratio 0.87 (95% CI: 0.83–0.91), $p<0.001$], change in $P_{ET}CO_2$ 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.

Again using categorical expressions for resting and CPX variables, multivariate Cox regression analysis results are listed in Table 6. $P_{ET}CO_2$ at the VT, rather than change in $P_{ET}CO_2$ or $P_{ET}CO_2$ at peak exercise, was included in the multivariate regression given its higher area under the ROC curve and hazard ratio. The VE/VCO_2 slope was the strongest predictor of 1-year cardiac-related events. Peak VO_2 and $P_{ET}CO_2$ 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.

Table 6
Multivariate Cox regression analysis

Variable	Chi-square	p-value
VE/VCO_2 slope[a]	39.1	<0.001
Variable	**Residual chi-square**	**p-value**
Peak VO_2[a]	7.4	0.007
$P_{ET}CO_2$ at VT[a]	4.3	0.04
LVEF	3.1	0.08
NYHA class	0.98	0.32
HF etiology (ischemic vs. non-ischemic)	0.45	0.50

[a] Variable retained in multivariate regression.

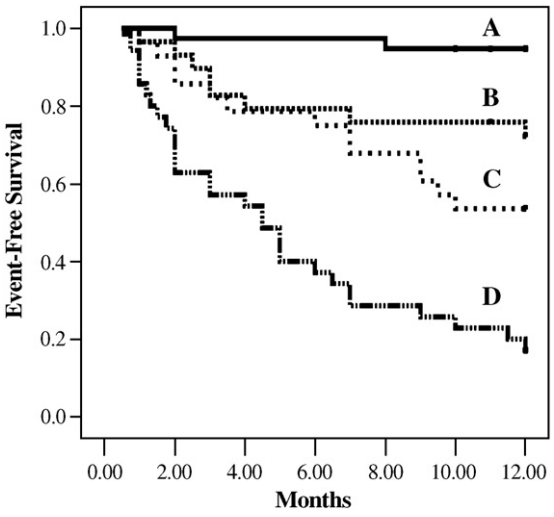

Fig. 1. Kaplan–Meier analysis.

Group	Characteristics	Subjects meeting criteria	Events	Percent event free
A	All three CPX variables normal	38	2	94.7
B	Only two CPX variables normal	29	8	72.4
C	Only one CPX variables normal	28	13	53.6
D	All three CPX variables normal	35	29	17.1

Log rank = 58.8, $p<0.0001$.
Cut points for CPX variables: VE/VCO2 slope < 34.4; Peak VO2 > 14.2 mlO2•kg^{-1}•min^{-1}; PETCO2 at VT > 36.1 mmHg.

Kaplan–Meier analysis results are illustrated in Fig. 1. Event-free survival characteristics were distinct among the four groups defined by the VE/VCO_2 slope, peak VO_2 and $P_{ET}CO_2$ at VT threshold values.

9. Discussion

The results of the present study indicate that $P_{ET}CO_2$ obtained during CPX has prognostic value in patients with HF. Specifically, the change in $P_{ET}CO_2$ from rest to the VT, $P_{ET}CO_2$ at the VT and $P_{ET}CO_2$ 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 $P_{ET}CO_2$ during CPX were significantly related to cardiac output and HF severity. In addition, Matsumoto et al. [9] concluded that decreased CO_2 production, abnormal ventilatory patterns (rapid and shallow breathing) and compensatory hyperventilation did not appear to explain the lower

$P_{ET}CO_2$ values during exercise in patients with HF, providing further support for lower cardiac output being the underlying cause. Given the relationship between $P_{ET}CO_2$ and both HF severity and cardiac output in these previous investigations, it is not surprising that PETCO2 demonstrated prognostic value in the present study.

While the change in $P_{ET}CO_2$ from rest to VT, $P_{ET}CO_2$ at VT and $P_{ET}CO_2$ at peak exercise were all significant univariate predictors of cardiac-related events, ROC curve analysis revealed that $P_{ET}CO_2$ at the VT was the strongest predictor of risk. The change in $P_{ET}CO_2$ from rest to VT is a reflection of increased pulmonary perfusion and therefore cardiac output with exercise. While the change in $P_{ET}CO_2$ 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 $P_{ET}CO_2$ during the initial stages of exercise, but still having an abnormally low $P_{ET}CO_2$ value at VT, are likely to have compromised cardiac function and therefore a poor prognosis. Additionally, a decrease in $P_{ET}CO_2$ beyond the VT would be expected as lactate accumulation stimulates a further increase in ventilation. The reduction in $P_{ET}CO_2$ from VT to peak is therefore not necessarily reflective of declining cardiac output. The prognostic significance of $P_{ET}CO_2$ at peak exercise is likely a reflection of it being lower throughout the exercise test (lower $P_{ET}CO_2$ at VT = lower $P_{ET}CO_2$ at peak). The additional influence of increased ventilation on $P_{ET}CO_2$ at peak exercise, a response which varies widely between individuals, has a potentially negative impact on its prognostic power. The ability of $P_{ET}CO_2$ 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 $P_{ET}CO_2$. Regardless of the underlying mechanism, $P_{ET}CO_2$ 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 VO_2. In recent years, a number of additional CPX variables have demonstrated prognostic value in the HF population. In particular, the VE/VCO_2 slope has been shown to be a superior prognostic variable compared to peak VO_2 in several previous investigations [5,7,21,22]. The results of the present study confirm the prognostic power of the VE/VCO_2 slope among variables obtained from CPX in patients with HF. In our multivariate regression analysis, both peak VO_2 and $P_{ET}CO_2$ at VT added prognostic value to the VE/VCO_2 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 VO_2 that have demonstrated prognostic value.

Our group has recently assessed the impact of time past CPX on the prognostic value of peak VO_2 and the VE/VCO_2 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 $P_{ET}CO_2$ 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 $P_{ET}CO_2$ 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 beta-blockade on the prognostic characteristics of CPX variables, primarily peak VO_2 [24–27]. These studies have generally found that peak VO_2 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 $P_{ET}CO_2$. Given the previously demonstrated link between cardiac output and $P_{ET}CO_2$ [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 $P_{ET}CO_2$ as well as other CPX variables.

In conclusion, previous studies have reported a strong relationship between $P_{ET}CO_2$ 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 $P_{ET}CO_2$, 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.

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