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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 $P_{ET}CO_2$ was determined immediately prior to the exercise test in the seated position. Peak oxygen consumption (VO_2) and the minute ventilation-carbon dioxide production (VE/VCO_2) 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 $P_{ET}CO_2$, peak VO_2 and VE/VCO_2 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 $P_{ET}CO_2$ (Chi-square = 28.4, $p < 0.001$), peak VO_2 (Chi-square = 21.6, $p < 0.001$) and VE/VCO_2 slope (Chi-square = 54.9, $p < 0.001$) were all significant predictors of cardiac related events. Multivariate Cox regression analysis revealed resting $P_{ET}CO_2$ added to the prognostic value of VE/VCO_2 slope in predicting cardiac related events (residual Chi-square = 4.4, $p = 0.04$). Peak VO_2 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 $P_{ET}CO_2$ may therefore be a valuable objective measure to obtain during both non-exercise and exercise evaluations in patients with HF.

Keywords: Heart failure; Risk factors; Exercise; Prognosis; Mortality; Ventilatory expired gas

1. Background

Several ventilatory expired gas variables obtained during exercise in addition to peak VO_2 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/VCO_2 slope), may be prognostically superior to peak VO_2 [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 ventilarory 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

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conducted. The resting partial pressure of end-tidal carbon dioxide ($P_{ET}CO_2$) may have prognostic value in patients with HF. Previous research has already demonstrated a significant relationship between $P_{ET}CO_2$ during exercise and cardiac function in patients with HF [7,8]. Numerous investigations have furthermore demonstrated a positive relationship between resting $P_{ET}CO_2$ 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 $P_{ET}CO_2$. In making this assumption, one can reasonably hypothesize a lower resting $P_{ET}CO_2$ 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 $P_{ET}CO_2$, 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 $P_{ET}CO_2$ 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 $P_{ET}CO_2$ 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 $P_{ET}CO_2$ 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 $mlO_2 \bullet kg^{-1} \bullet min^{-1}$ 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 $P_{ET}CO_2$ was defined as the two-minute averaged value prior to exercise testing in the seated position. Oxygen consumption ($ml \bullet kg^{-1} \bullet min^{-1}$), VCO_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 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 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 $P_{ET}CO_2$ 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 $P_{ET}CO_2$, peak VO_2 and VE/VCO_2 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 $P_{ET}CO_2$, peak VO_2 and VE/VCO_2 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 upon the optimal threshold value of resting $P_{ET}CO_2$ and VE/VCO_2 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 $P_{ET}CO_2$ and VE/VCO_2 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.

Table 1
Subject characteristics

Number of subjects	121 (76 male/45 female)
Age (years)	49.3 ± 14.7
Body mass index (kg/m^2)	28.7 (±6.8)
Left ventricular ejection fraction (%)[£]	28.4% ± 13.4
New York Heart Association Class (number of subjects)	
Class I	22
Class II	35
Class III	64
Heart failure etiology (ischemic/non-ischemic)	51/70
ACE inhibitor (number of subjects)	92
Cardiac glycoside (number of subjects)	90
Diuretic (number of subjects)	100
Nitrate (number of subjects)	29
Beta-blocker (number of subjects)	59

£: Determined by two-dimensional echocardiography.

Table 2
Key ventilatory expired gas variables

Variable	Mean ± Standard Deviation
Resting $P_{ET}CO_2$ (mmHg)	34.1 ± 4.6
Peak VO_2 ($ml•kg^{-1}•min^{-1}$)	14.5 ± 5.1
VO_2 at VT ($ml•kg^{-1}•min^{-1}$)	11.6 ± 3.9
VE/VCO_2 Slope	35.9 ± 8.7
Peak RER	1.05 ± 0.1
Resting oxygen pulse (ml/beat)	4.0 ± 1.5
Peak oxygen pulse (ml/beat)	10.1 ± 4.0
Resting VD/VT	0.37 ± 0.07
Peak VD/VT	0.25 ± 0.07

3. Results

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

Table 3
Pearson product moment correlation between resting $P_{ET}CO_2$ and key variables

	Resting $P_{ET}CO_2$
Age	−0.10
Left ventricular ejection fraction	0.13
Body mass index	0.34*
VE/VCO_2 slope	−0.62*
Peak VO_2	0.32*
Resting oxygen pulse	0.39*
Peak oxygen pulse	0.36*
Resting VD/VT	−0.30*
Peak VD/VT	−0.35*

* $p < 0.001$.

Table 4
Univariate and multivariate Cox Regression Analysis for one-year cardiac-related events

Predictor variable	Chi-square	p-value
Univariate analysis		
Body mass index	0.82	0.37
Left ventricular ejection fraction	3.7	0.06
Beta-blockade use	0.44	0.51
New York Heart Association Class	17.6	<0.001*
Resting $P_{ET}CO_2$	28.4	<0.001*
VE/VCO_2 slope	54.9	<0.001*
Peak VO_2	21.6	<0.001*
Multivariate analysis		
VE/VCO_2 slope	54.9	<0.001*
Resting $P_{ET}CO_2$	4.4	0.04*
New York Heart Association Class	4.4	0.04*
Peak VO_2	0.07	0.80

* Statistically significant.

hemodymanic 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 $P_{ET}CO_2$ was not significantly correlated with age or LVEF. The relationship between resting $P_{ET}CO_2$ 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 $P_{ET}CO_2$, 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 $P_{ET}CO_2$ 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.

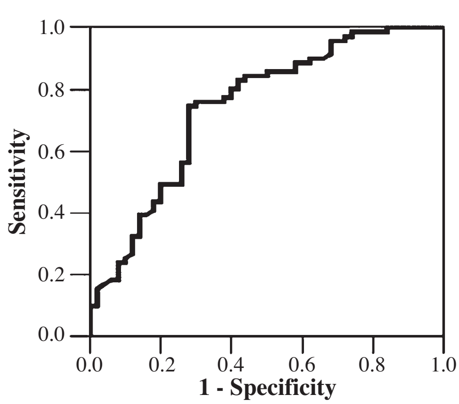

Fig. 1. Receiver operating characteristic curve analysis for one-year cardiac related events: resting $P_{ET}CO_2$

Variable	Area under the curve	95% Confidence interval	p-value
Resting $P_{ET}CO_2$	0.74	0.63–0.84	$p<0.001$

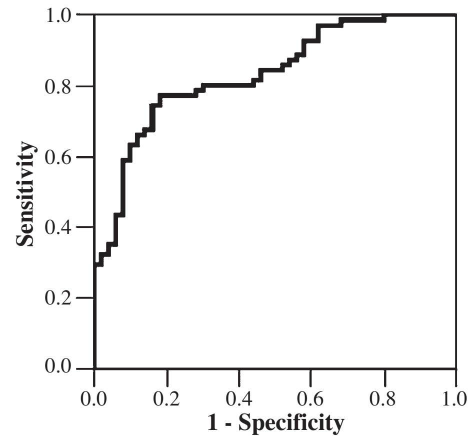

Fig. 2. Receiver operating characteristic curve analysis for one-year cardiac related events: VE/VCO_2 slope

Variable	Area under the curve	95% Confidence interval	p-value
VE/VCO_2 slope	0.84	0.76–0.92	$p<0.001$

Receiver operating characteristic curves for resting $P_{ET}CO_2$ and VE/VCO_2 slope as continuous variables are illustrated in Figs. 1 and 2, respectively.

Optimal threshold values for resting $P_{ET}CO_2$ (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 $P_{ET}CO_2$ and VE/VCO_2 slope threshold values are listed in Table 5.

Kaplan Meier analyses using the predetermined threshold values of resting $P_{ET}CO_2$ alone, VE/VCO_2 slope alone and resting $P_{ET}CO_2$ combined with VE/VCO_2 slope are illustrated in Figs. 3–5.

Using the optimal resting $P_{ET}CO_2$ threshold value as determined by ROC curve analysis, sixty-seven subjects

Table 5
Univariate hazard ratios for resting $P_{ET}CO_2$ (greater value preferred) and VE/VCO_2 slope (lesser value preferred) threshold values

End point	Threshold criteria	Hazard ratio	p-value
Cardiac-related Events (1 yr)	Resting $P_{ET}CO_2 \leq 33.0$ = negative prognosis	4.8	<0.0001
Cardiac-related Events (1 yr)	VE/VCO_2 slope ≥ 34.4 = negative prognosis	7.2	<0.0001

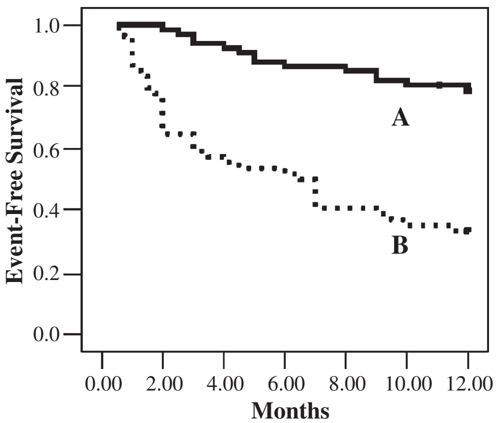

Fig. 3. Kaplan–Meier analysis for one-year cardiac-related events using a resting $P_{ET}CO_2$ threshold of ≤/>33.0 mmHg.Legend for Fig. 3

Group	Characteristics	Subjects meeting criteria	Events	Percent event free
A	Resting $P_{ET}CO_2 > 33.0$ mmHg	67	$14^{\dagger}$	79.1%
B	Resting $P_{ET}CO_2 \leq 33.0$ mmHg	54	$36^{£}$	33.3%

Log rank=31.0, $p<0.0001$. •=Censored cases. †=2 cardiac-related deaths and 12 cardiac- related hospitalizations. £=7 cardiac-related deaths and 29 cardiac-related hospitalizations.

demonstrated a favorable resting $P_{ET}CO_2$ 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 $P_{ET}CO_2$ value was 79.1% and 33.3% respectively. Using the optimal VE/VCO_2 slope threshold value as determined by ROC curve analysis, sixty-two subjects demonstrated a favorable VE/VCO_2 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/VCO_2 slope value was 85.5% and 30.5% respectively. When combining resting $P_{ET}CO_2$ with VE/VCO_2 slope, forty-eight subjects demonstrated favorable values for both variables, thirty-three subjects demonstrated one unfavorable value (resting $P_{ET}CO_2$ or VE/VCO_2 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.

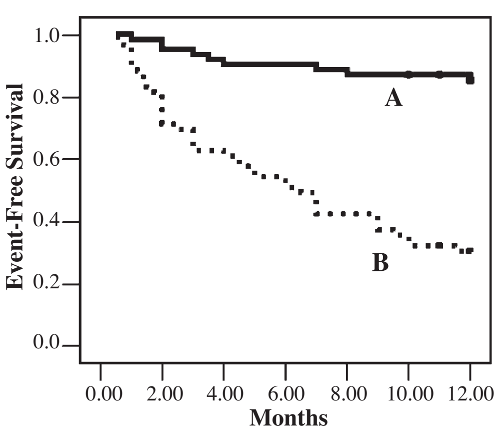

Fig. 4. Kaplan-Meier analysis for one-year cardiac-related events using a VE/VCO_2 slope threshold of</≥34.4 mmHg.Legend for Fig. 4

Group	Characteristics	Subjects meeting criteria	Events	Percent event free
A	VE/VCO_2 slope<34.3	62	$9^{\dagger}$	85.5%
B	VE/VCO_2 slope≥34.3	59	$41^{£}$	30.5%

Log rank=.6, $p<0.0001$. •=Censored cases. †=0 cardiac-related deaths and 9 cardiac-related hospitalizations. £=9 cardiac-related deaths and 32 cardiac related hospitalizations

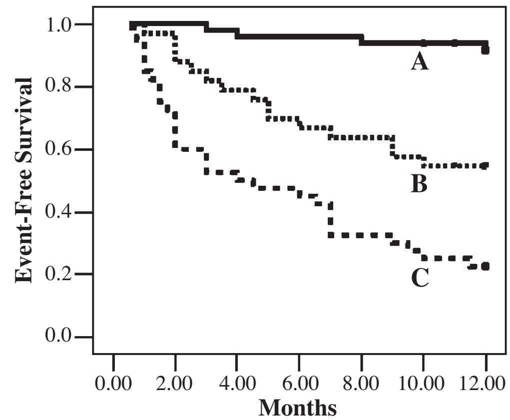

Fig. 5. Kaplan-Meier analysis for one-year cardiac-related events using resting $P_{ET}CO_2$ threshold of ≤/>33.0 mmHg and VE/VCO_2 slope threshold of</≥34.4.Legend for Fig. 5

Group	Characteristics	Subjects meeting criteria	Events	Percent event free
A	Resting $P_{ET}CO_2 > 33.0$ mmHg and VE/VCO_2 slope<34.4	48	$4^{\dagger}$	91.7%
B	Resting $P_{ET}CO_2 = 33.0$ mmHg or VE/VCO_2 slope≥34.4	33	$15^{£}$	54.5%
C	Resting $P_{ET}CO_2 \leq 33.0$ mmHg and VE/VCO_2 slope≥34.4	40	31	22.5%

Log rank=50.9, $p<0.0001$. •=censored cases. †=0 cardiac-related deaths and 4 cardiac-related Hospitalizations. £=2 cardiac-related deaths and 13 cardiac-related hospitalizations.=7 cardiac-related deaths and 24 cardiac related hospitalizations.

4. Discussion

The results of the present study indicate that resting $P_{ET}CO_2$ 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 $P_{ET}CO_2$ and either age or LVEF. A significant positive correlation between resting $P_{ET}CO_2$ and BMI was, however, apparent. This relationship indicates individuals with a higher BMI tended to have a more favorable resting $P_{ET}CO_2$ 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 combination with an established clinical (NYHA class) and ventilatory expired gas (VE/VCO_2 slope) variable. Acquisition 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 ($R2=0.82$, $p<0.01$). 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 Idris 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 demonstrated 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 association 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, echocardiography [3,24–26], ECG [26–30], blood pressure [31–33] and inflammatory [34–37] and neurohormonal blood markers, [38,39] have been shown to provide information pertinent to prognosis and disease severity and are therefore frequently ascertained during clinic 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 standard 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 VO_2, a number of recent investigations have challenged its prognostic power relative to other CPET variables, particularly the VE/VCO_2 slope [3–6,42–44]. The results of the present study are consistent with these recent investigations in that the VE/VCO_2 slope had greater prognostic power than peak VO_2. Peak VO_2 has two potential limitations when assessing prognosis. First, a true assessment of peak VO_2 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 ≥ 1.0. A second potential limitation is the contribution peripheral metabolism has on peak VO_2. This contribution is made apparent by investigations demonstrating that high values for peak VO_2 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 VO_2. This issue was raised by the work of Wilson et al. [47] who reported that among 64 patients evaluated for heart transplantation, cardiac output and pulmonary wedge pressure responses to exercise differed markedly despite patients having similar values for peak VO_2. These results additionally indicate that resting $P_{ET}CO_2$ may add prognostic value when assessed in combination with the VE/VCO_2 slope in estimating risk in HF, a finding that has not been previously reported. Both resting $P_{ET}CO_2$ and the VE/VCO_2 slope are not influenced by subject effort, which may be a primary reason for their superior prognostic value compared to peak VO_2. As this type of evidence continues to mount, consideration should be given to revising established guidelines, which presently recommend only the assessment of peak VO_2 for risk stratification in HF [40,41]. Specifically, the VE/VCO_2 slope appears to be the superior prognostic CPET variable. If future research supports our findings, the inclusion of resting $P_{ET}CO_2$ 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/VCO_2 slope and peak VO_2 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/VCO_2 slope and resting $P_{ET}CO_2$ 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 VO_2 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 $P_{ET}CO_2$, cardiac function and outcomes, as well as the impact of beta-blockade use, is needed before a universal recommendation for including resting $P_{ET}CO_2$ 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.

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