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Clinical Trials

Development of a Cardiopulmonary Exercise Prognostic Score for Optimizing Risk Stratification in Heart Failure: The (P)e(R)i(O)dic (B)reathing During (E)xercise (PROBE) Study

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ABSTRACT

Background: Cardiopulmonary exercise testing (CPET) provides powerful information on risk of death in heart failure (HF). We sought to define the relative and additive contribution of the 3 landmark (CPET) prognostic markers—peak oxygen consumption (VO_2), minute ventilation/carbon dioxide production (VE/VCO_2) slope, and exercise periodic breathing (EPB)—to the overall risk of cardiac death and to develop a prognostic score for optimizing risk stratification in HF patients.
Methods and Results: A total of 695 stable HF patients (average LVEF: 25 ± 8%) underwent a symptom-limited CPET maximum test after familiarization and were prospectively tracked for cardiac mortality. At multivariable Cox analysis EPB emerged as the strongest prognosticator. Using a statistical bootstrap technique (5000 data resamplings), point estimates, and 95% confidence intervals were obtained. Thirty-two configurations were adopted to classify patients into a given cell, according to EPB presence or absence and values of the 2 other covariates. Configurations without EPB and with VE/VCO_2 slope ≤30 were not significantly different from 0 (reference value). Statistical power of configurations increased with higher VE/VCO_2 slope and lower peak VO_2. This prompted us to formulate a score including EPB as a discriminating variable, the (P)e(R)i(O)dic (B)reathing during (E)xercise (PROBE), which ranges between -1 and 1, with zero as reference configuration, that would help to optimize the prognostic accuracy of CPET-derived variables. The greatest PROBE score impact was provided by EPB, followed by VE/VCO_2 slope, whereas peak VO_2 added minimal prognostic power.
Conclusions: EPB with an elevated VE/VCO_2 slope leads to the highest and most precise PROBE score, whereas no additional risk information emerges when EPB is present with a peak VO_2 ≤10 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$. PROBE score appears to provide a step forward for optimizing CPET use in HF prognostic definition. (*J Cardiac Fail 2010;■:1–7*)
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The growing and extensive application of cardiopulmonary exercise testing (CPET) techniques in daily clinical practice is supported by an abundant amount of research on its prognostic value in patients with heart failure (HF).[1–5] Among the large series of variables identified and proposed for risk definition, studies have consistently demonstrated that the occurrence of exercise periodic breathing (EPB) may provide robust prognostic resolution[6–8] with notable discriminating power for arrhythmic versus cardiac pump failure death compared with established CPET prognosticators such as peak oxygen consumption (VO_2) and the minute ventilation/carbon dioxide production (VE/VCO_2) slope.[9]

Although it is conceivable that combining several CPET variables may improve the predictive value of any individual response and some algorithms have been proposed,[10,11] we are unaware of previous attempts to assess the combined prognostic application of EPB, peak VO_2, and the VE/VCO_2 slope. This may have relevant impact in terms of a more appropriate and comprehensive approach for the follow-up of patients with different degrees of HF and may represent a compelling step forward in the optimization of CPET applicability in the HF population.

Therefore, the present study had 2 aims: 1) to verify the independent prognostic role of EPB compared with peak VO_2 and the VE/VCO_2 slope; and 2) to define the relative and additive contributions of these variables to the overall estimation of risk for cardiac death by developing a prognostic score using these variables.

Methods

This was a multicenter study consisting of HF patients from the cardiopulmonary exercise laboratories at San Paolo Hospital, Palo Alto Health Care System, Palo Alto, CA; Virginia Commonwealth University, Richmond, VA; and the LeBauer Cardiovascular Research Foundation, Greensboro, NC. Six hundred and ninety-five subjects diagnosed to have HF, who underwent a symptom-limited CPET between June 1998 and June 2007, were included. Subjects with significant obstructive lung disease evidenced by a forced vital capacity in 1 second ≤70% or who were unable to perform a maximal exercise test were excluded from the study. Smokers were 15% to 20% of the population and were distributed similarly across different subgroups. All patients were in New York Heart Association functional Classes I to III. All subjects completed a written informed consent and Institutional Review Board approval was obtained at each institution.

CPET Procedure and Data Collection

Symptom-limited CPET was performed in all patients. Each center used conservative ramping protocols and maximal tests were individualized to target an exercise duration between 8 and 10 minutes. The test was considered maximal for the respiratory exchange ratio (RER) ≥1.08 and this cutoff was considered as inclusion criteria. Centers in the United States primarily used a treadmill; the Italian center solely used a cycle ergometer. A potential prognostic bias because of the different exercise modes can reasonably be excluded given that in a previous study these 2 modes of exercise provided identical predictive cutoff values for peak VO_2 and the VE/VCO_2 slope.[12] Ventilatory expired gas analysis was performed using a metabolic cart at all 4 centers (Medgraphics CPX-D, Minneapolis, MN, or Sensormedics Vmax29, Yorba Linda, CA).

Standard 12-lead electrocardiograms were obtained at rest, each minute during exercise, and for at least 5 minutes during the recovery phase; blood pressure was measured using a standard cuff sphygmomanometer. Minute ventilation (VE, body temperature, atmospheric pressure saturated with water vapour), oxygen uptake (VO_2, standard temperature and pressure dry), carbon dioxide output (VCO_2, standard temperature and pressure dry), and other cardiopulmonary variables were acquired breath-by-breath, averaged over 30 seconds, and printed in rolling averages every 10 seconds. The V-slope method was used to measure the anaerobic threshold.[13]

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 of our group and others has shown this method of calculating the VE/VCO_2 slope to be optimal for estimating prognosis.[14–16] Ten-second averaged VE data were also analyzed to determine if a subject demonstrated EPB. EPB was defined as an oscillatory pattern at rest that persisted for ≥60% of the exercise test at an amplitude ≥15% of the average resting value.[8,9] This analysis was carried out by a quite rapid manual calculation. Test termination criteria consisted of patient request, ventricular tachycardia, ≥2.0 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.

Event Tracking

Subjects were followed for cardiac mortality via hospital and outpatient medical chart review. Subjects were followed by the HF programs at their respective institution, providing a high likelihood that all events were captured. Any death with a cardiac-related discharge diagnosis was considered an event. Clinicians conducting the exercise tests were not involved in decisions regarding cause of death. Subjects suffering a non-cardiac death or undergoing a heart transplant or left ventricular assist device implantation were treated as censored cases at the time of the event.

Statistical Analysis

The main study end point was cardiac-related mortality. The prognostic value of EPB, the VE/VCO_2 slope, and peak VO_2 was first investigated by univariate analysis. Survival curves were constructed using the Kaplan-Meier method and compared by the log-rank test. The joint prognostic role of the covariates was then evaluated by multivariable Cox models. Because the 3 covariates were considered as categorical, they were included into Cox model by means of indicator variables, considering the better putative prognostic category as the reference. The prognostic contribution of each covariate was evaluated by the Wald test.

The Cox model is the common procedure to evaluate the prognostic impact of clinical covariates providing an indicator (hazard ratio), which is a measure of the hazard from a given configuration of covariate values with respect to a reference value. The major limitation of this indicator is the lack of normalization (ie, the absence of a defined range of variation), which prevents an objective judgment of the clinical relevance of the risk associated with a given hazard ratio.

Score Development

The statistical procedure for developing a score was obtained from both coefficients and their standard deviations (SDs) from the multivariable Cox model. We considered multiclass covariates as a set of indicator variables. A total of 32 configurations were adopted to classify patients into a given cell according to the value of the 3 covariates: EPB, VE/VCO_2 slope, and peak VO_2. Covariates were categorized as follows: EPB (0 = no; 1 = yes); VE/VCO_2 slope (0 = ≤30; 1 = 30−36; 2 = 36−45; 3= >45 according to the multilevel ventilatory classification recently proposed by Arena et al[5]); and peak VO_2 (0 = <20 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$; 1 = 15−20 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$; 2 = 10−15 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$; and 3 = ≤10 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$, according to the Weber classification.[17]

The score was then obtained as a normalized linear combination of the weighted Cox regression coefficients, where the weights were the SDs of the coefficients. The normalized values were obtained by means of the arc-tangent transform.

According to this procedure a new prognostic indicator, (P)e(R)i(O)dic (B)reathing during (E)xercise (PROBE), was obtained which results in a normalized range (−1 to 1), with zero the value for the reference covariates (Figure 1). This normalization property allows an immediate objective evaluation of the risk associated with a given value of the PROBE indicator. Starting from the basic dataset (695 patients), points estimates, and 95% confidence intervals were obtained by bootstrap technique based on 5000 resamplings. An internal validation was obtained by assessing the score confidence intervals. The predictive capability of the model was evaluated by the Harrell's C index, an extension of area under the receiver operating characteristic curve for survival data.[18] The predicted incidence of death at 24 months was obtained including the score in a Cox regression model; the nonlinear relationship between log (HR) and score was taken into account by using a 3 knots restricted cubic spline function.

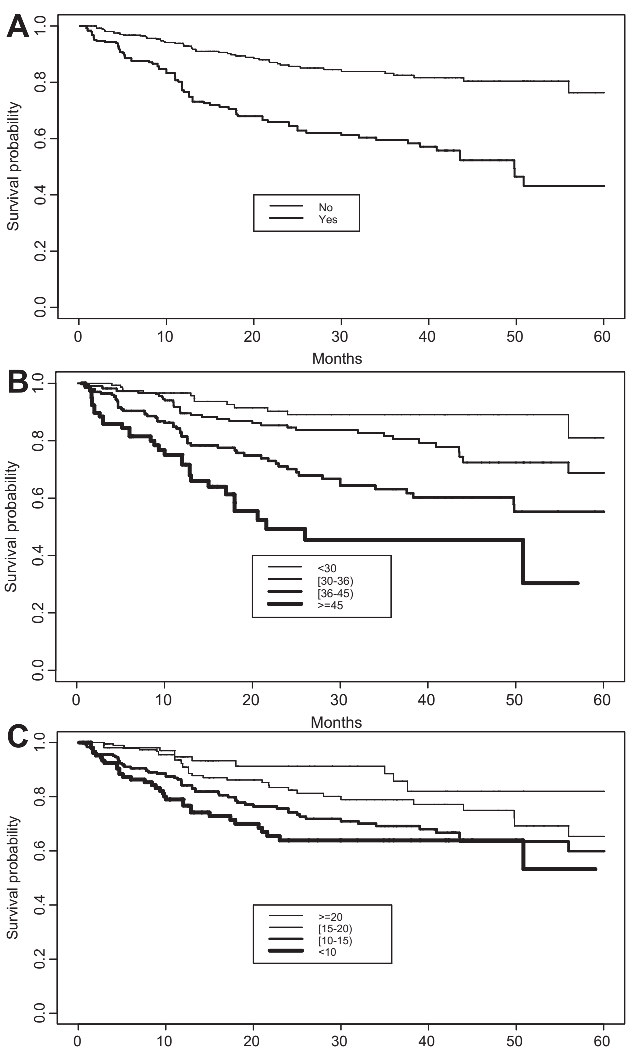

Fig. 1. Kaplan-Myers survival curves according to exercise periodic breathing (A), ventilation to carbon dioxide slope (B), and peak oxygen consumption (C).

Table 1. Demographic and Clinical Characteristics

Age, y	56.0 ± 13.4
Gender (male/female), %	71/29
Left ventricular ejection fraction, %	25.3 ± 7.9
NYHA (average)	2.4 ± .76
Heart rate at rest, beats/min	74 ± 24
Blood pressure at rest, mm Hg	
Systolic	118 ± 25
Diastolic	72 ± 24
Etiology	
Ischemic, %	50
Hypertensive, %	20
Postmyocarditis, %	10
Idiopathic, %	20
Drug therapy distribution	
Prescribed ACE inhibitor, %	77
Prescribed diuretic, %	76
Prescribed β-blocker, %	73
Prescribed antialdosterone agents, %	50
Prescribed inotropic agents, %	40
CPET variables	
Peak VO_2, mL $O_2 \cdot kg^{-1} \cdot min^{-1}$	15 ± 5
Peak RER	1.14 ± 0.5
VE/VCO_2 slope	36 ± 7

ACE, angiotensin-converting enzyme; CPET, cardiopulmonary exercise testing; NYHA, New York Heart Association; RER, respiratory exchange ratio; VO_2, peak oxygen consumption; VE/VCO_2, ventilation to carbon dioxide.

Results

The case series comprised 695 patients; 31% from Italy (Cardiopulmonary Laboratory at S. Paolo Hospital, Milano) and 61% from the United States (23% from Virginia Commonwealth University; 26% from Palo Alto Health System Care and 20% from the LeBauer Research Foundation). Table 1 shows the baseline clinical characteristics of patient population. Distribution of the covariates is shown in Table 2. The median follow-up time was 24 months and there were 134 cardiac-related deaths during this period.

Table 2. Case Series Distribution according to EPB, VE/VCO_2 Slope, and Peak VO_2

Covariates	n	(%)
EPB		
No	444	64
Yes	251	36
VE/VCO_2 slope		
<30	176	25
30−36	230	33
36−45	206	30
≥45	83	12
Peak VO_2		
≥20	118	17
15−20	211	30
10−15	255	37
≥10	111	16

EPB, exercise periodic breathing; VO_2, peak oxygen consumption; VE/VCO_2, ventilation to carbon dioxide.

Table 3. Multivariable Cox Model

Covariates	Hazard Ratio	95% Confidence Interval	Wald Test
EPB			19.5, $P < .0001$
No	1	—	
Yes	2.2	1.6–3.2	
VE/VCO_2 slope			25.7, $P < .0001$
<30	1	—	
30–36	1.7	0.9–3.2	
36–45	2.7	1.4–5.0	
≥45	4.9	2.4–9.9	
Peak VO_2			2.8, $P = .42$
≥20	1	—	
15–20	1.6	0.8–3.2	
10–15	1.8	0.9–3.6	
<10	1.6	0.8–3.5	

EPB, exercise periodic breathing; VO_2, peak oxygen consumption; VE/VCO_2, ventilation to carbon dioxide.

By univariate analysis, EPB, the VE/VCO_2 slope, and peak VO_2 all demonstrated significant prognostic value. Kaplan-Meier curves for the 3 variables are reported in Figure 1. Significant differences were observed for presence of EPB, between ventilatory classes, and peak VO_2 classifications (log rank test = 47.3, $P < .0001$; 57.5, $P < .0001$ and 21.9, $P < .0001$, respectively).

Results of the multivariable Cox model are shown in Table 3. Both EPB and the VE/VCO_2 slope retained significant prognostic power, whereas the contribution of peak VO_2 was no longer statistically significant. Notably, when the VE/VCO_2 slope and VO_2 were compared in a bivariate Cox model, only the prognostic contribution of the VE/VCO_2 slope was statistically significant (Wald test for VE/VCO_2 slope = 33.78; $P < .0001$; and for peak VO_2 = 5.90; $P = .11$).

Considering 2 classes for EPB (yes/no) and 4 classes for peak VO_2[17] and VE/VCO_2 slope,[5] 32 configurations were obtained. Table 4 provides the PROBE score configurations and the 95% confidence intervals, also shown in Figure 2 (smoothed patterns). Score configurations without EPB and with VE/VCO_2 slope ≤30 were not significantly different from 0 (score of the reference configuration). The PROBE score increased when EPB changed from absent to present, with the increase of the VE/VCO_2 slope and the decrease of peak VO_2. The greatest score impact was provided by EPB, followed by VE/VCO_2 slope, whereas minor risk influence was provided by peak VO_2. Figure 3 report the mortality rate in relation to the score configuration.

How to Use the Probe Score

An example of how to use the proposed score may be a HF patient with EPB, a VE/VCO_2 slope of 29, and a peak VO_2 of 12 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$. Looking at Table 4, the patient presents with a combination 1-0-2 (see table legend), which corresponds to a configuration number of 19 (Table 4). This configuration yields to a PROBE score of 0.885 (Table 4). To weight the cardiac mortality incidence of a patient with a configuration of 19, we may then refer to Figure 3, which shows a mortality incidence of 0.294.

Table 4. Probe score (and 95% Confidence Interval) for the Configurations Given by the Combinations of EPB, VE/VCO_2 Slope and Peak VO_2

Configuration Number	EPB	VE/VCO_2 slope	Peak VO_2	No. Pts	PROBE Score	Predicted Incidence of Death at 24 Months	95% Confidence Interval	
1	0	0	0	59	0	0.024	—	—
2	0	0	1	61	0.465	0.051	−0.401	0.782
3	0	0	2	24	0.556	0.060	−0.189	0.794
5	0	1	0	35	0.560	0.061	−0.200	0.802
6	0	1	1	60	0.739	0.110	0.345	0.868
7	0	1	2	46	0.774	0.133	0.522	0.871
8	0	1	3	11	0.730	0.105	0.315	0.866
9	0	2	0	10	0.781	0.138	0.592	0.857
10	0	2	1	31	0.839	0.205	0.693	0.900
11	0	2	2	49	0.852	0.226	0.743	0.902
12	0	2	3	14	0.837	0.202	0.698	0.898
15	0	3	2	14	0.886	0.296	0.83	0.918
16	0	3	3	20	0.878	0.277	0.818	0.913
19	1	0	2	15	0.885	0.294	0.820	0.920
22	1	1	1	16	0.905	0.344	0.849	0.935
23	1	1	2	48	0.910	0.358	0.868	0.935
24	1	1	3	10	0.905	0.344	0.856	0.933
26	1	2	1	26	0.923	0.396	0.890	0.943
27	1	2	2	39	0.926	0.405	0.900	0.943
28	1	2	3	30	0.923	0.396	0.895	0.941
31	1	3	2	20	0.935	0.434	0.916	0.949
32	1	3	3	20	0.933	0.427	0.914	0.947

EPB, exercise periodic breathing; PROBE, (P)e(R)i(O)dic (B)reathing during (E)xercise; Pts, patients; VO_2, peak oxygen consumption; VE/VCO_2, ventilation to carbon dioxide.

Covariates' categories are reported as follows: EPB: 0 = no; 1 = yes; VE/VCO_2 slope: 0= ≤30; 1 = 30–36; 2 = 36–45; 3 = ≥45; peak VO_2: 0: ≥20 $mL \cdot kg^{-1} \cdot min^{-1}$; 1 = 15–20 $mL \cdot kg^{-1} \cdot min^{-1}$); 2 = 10–15 $mL \cdot kg^{-1} \cdot min^{-1}$) 3 = ≤10 $mL \cdot kg^{-1} \cdot min^{-1}$.

Configurations with n patients < 10 (ie, < 2%) are not reported.

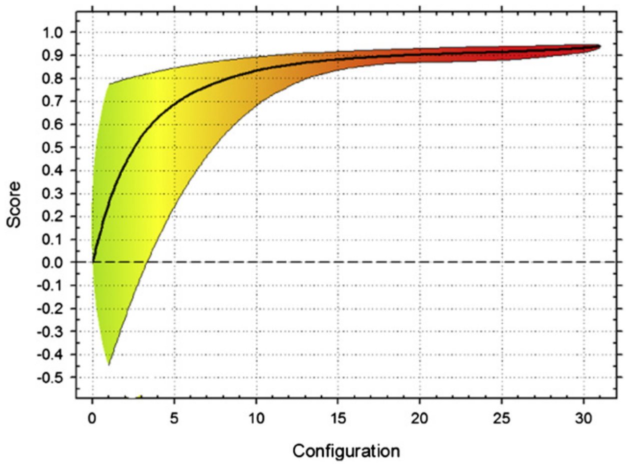

Fig. 2. Smoothed shapes of score (bold line) and 95% confidence interval (thin lines) according to configurations given by the covariate patterns. See Table 4 for the correspondence between the various configurations of exercise periodic breathing, ventilation to carbon dioxide slope, and peak oxygen consumption and the text (Results section) for the explanation on how to use this plot.

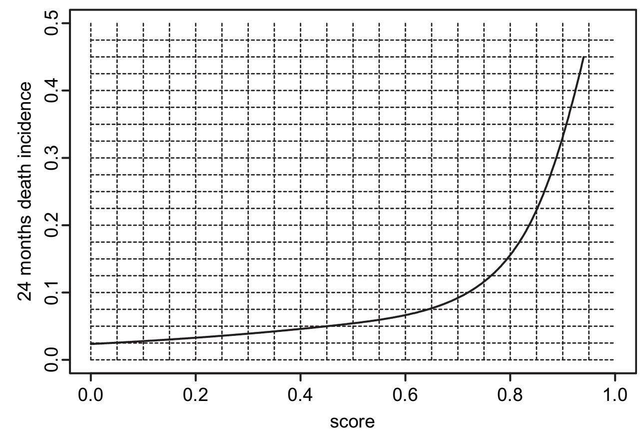

Fig. 3. Plot relating the score configuration and mortality incidence. See text for explanation (Results section)

Discussion

EPB is an abnormal pathophysiological phenomenon that occurs at a rate that varies from 18% to 30% across different HF populations and carries key information on the clinical evolution of HF syndrome.[6–9,19–21] The pathogenesis of EPB, although complicated, seems to derive from a combination of deregulatory pathways involved in the mechanical and neural feedback control of the cardiopulmonary system.[19,20] EPB prevalence is similar in both systolic and diastolic HF.[22] Present observations add some novel and potentially useful clinical insights for optimizing CPET use in clinical daily practice.

EPB emerged as the strongest CPET-derived variable predictive of cardiac outcome. This prompted us to refine the clinical application of this observation and to formulate a score, the PROBE, which includes EPB as a discriminating variable and helps to optimize the prognostic accuracy of actual CPET reference variables such as peak VO_2 and VE/VCO_2 slope. With this aim, the predictive accuracy of the PROBE score was then tested by stratifying patients by VO_2 functional impairment according to the Weber classification (A to D)[17] and the recently proposed ventilatory classification (I to IV) based on the VE/VCO_2 slope.[5]

PROBE Analysis According to Weber Classification

As originally proposed, the Weber classification has been considered a standard for grading functional and cardiac impairment during maximal exercise in patients with HF. This classification was based on the elegant demonstration that functional impairment indicated by a low peak VO_2 invariably depicts a failure of cardiac output to properly augment during incremental exercise.

The series of studies that applied the Weber classification clearly demonstrated that the use of various peak VO_2 cut points may not provide definitive prognostic indications except for patients with severely compromised aerobic performance and a peak $VO_2 \leq 10$ mL $O_2 \cdot kg^{-1} \cdot min^{-1}$,[23–25] even when chronic use of β-blockers is taken into account.[24] Guidelines have thus adopted this evidence suggesting that a peak $VO_2 \leq 10$ mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ and documentation of anaerobic metabolism occurrence is an absolute indication for heart transplantation.[26]

In the present investigation, stratification by peak VO_2 did not add to EPB prediction of outcome and the PROBE combinations that included different levels of peak VO_2 were not significant. This was also the case for HF patients with a peak $VO_2 \leq 10$ mL $O_2 \cdot kg^{-1} \cdot min^{-1}$, a finding that may appear conflicting with current clinical recommendations. Indeed, among the 111 patients with a peak VO_2 ≤ 10 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$, all but 1 subject presented with EPB, suggesting that in the advanced stages of the disease a severely low peak VO_2 and EPB coexistence is a likely scenario. Conversely, it is interesting to consider that in the very rare situation in which a low peak VO_2 is not associated with EPB, prognosis is relatively favorable. Thus, an important practical implication of our findings is that, in the complex and integrated process of clinical decision-making, a low peak VO_2 would indicate a high mortality risk, especially in the presence of EPB.

PROBE Analysis According to Ventilatory Classification

Attempts to define CPET validity for predicting risk among HF patients with intermediate exercise intolerance (peak $VO_2 \geq 10 \leq 18$ mL $O_2 \cdot kg^{-1} \cdot min^{-1}$) have evolved to include markers of ventilatory inefficiency and VE/VCO_2 slope has become a standard marker for risk prediction in this category of patients.[2–5] We recently assessed the prevalence and prognostic utility of a heightened VE/VCO_2 slope in combination with EPB in a large cohort of HF patients.[8] Interestingly, an equivalent distribution was observed between patients presenting with a high VE/VCO_2 slope but no EPB or with EPB and a normal VE/VCO_2 slope or with both abnormal.

Thus, contrary to what may be expected, a high VE/VCO_2 slope is not necessarily associated with EPB. When both of these abnormalities are present, the extent of underlying pathophysiological abnormalities (primarily involving the central and peripheral control of ventilation), represents a very high level of risk. However, in our previous study, as in others,[2–4,27,28] the VE/VCO_2 slope was considered as a dichotomous variable with a threshold of 34 for increased cardiac mortality. More recently, the VE/VCO_2 slope was analyzed as a continuous variable and a ventilatory classification was proposed[5]. The present findings underscore the importance of assessing ventilatory inefficiency according to a multilevel classification and provide an argument for identifying and close monitoring of patients with a combination of EPB and increased ventilatory responses to exercise.

Other CPET Scores

Most of the available scores derived from multivariable statistical techniques have been derived from standard exercise testing among coronary artery disease patients and without gas exchange analysis. Few studies have been developed that include CPET variables for risk stratification among HF patients. Aaronson et al[29] developed and validated a model using a series of noninvasive and invasive variables in combination with peak VO_2. Myers et al[30] recently proposed a comprehensive CPET score including additional CPET-derived variables such as end-tidal of CO_2. When we compared the PROBE score with Myers's score, the receiver operating characteristic analysis showed a similar Confidence Interval index score (0.71 versus 0.75) with a 95% confidence interval of 0.67 to 0.76 indicating an equivalent power to predict events. None of the previous studies, however, included EPB in its respective multivariate analysis. One limitation of the PROBE score would be the limited number of variables included in the model. However, our goal was to specifically optimize the use of CPET variables that have become well established over the last decade. In addition, an analysis focused on few, but prognostically strong parameters, is likely to be simpler, more time-efficient, and easily repeatable across different laboratories.

Study Limitations

The PROBE score did not consider other reported CPET-derived variables that have been shown to be prognostic. In particular, we did not include the oxygen uptake efficiency slope, a variable that has received some recent attention.[31,32] Nonetheless, the VE/VCO_2 slope might be even a superior prognostic marker compared with the oxygen uptake efficiency slope.[33]

Both oxygen uptake efficiency slope and PROBE score calculations require some computations that can easily run by computer software packages of metabolic systems.

In addition, our study comprised patients with moderate HF, largely with an ischemic etiology and largely male. At variance with previously proposed algorithms,[10] the performance of EPB in different subpopulations of HF has not been explored, and both EPB and the PROBE score require validation in external cohort of patients. Finally, future study would have to be planned to assess the potential incremental value of the exercise score versus common clinical measures such as renal function, blood pressure, heart rate, and clinical measures.

Conclusions and Perspectives

The present results underscore the importance of systematic recognition, analysis, and reporting of EPB occurrence in the CPET summary report. EPB alone is a strong prognostic marker, but when combined with other established CPET variables, the prognostic power of CPET is enhanced. The value of EPB is supported by the following: 1) PROBE scores excluding EPB were not significant predictors of risk with the exception of patients with a high VE/VCO_2 slope; 2) in patients already at high risk (VE/VCO_2 slope ≥ 30), EPB provides additional prognostic information; and 3) when EPB is present with a peak VO_2 ≤ 10 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$, the score configuration does not provide additive information to EPB alone. Thus, although the proposed score requires validation in other samples, it may be viewed as a step forward in the effort to optimize the role of CPET in the clinical decision making of patients with HF.

Disclosures

None.

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