The Lowest VE/VCO_2 Ratio During Exercise as a Predictor of Outcomes in Patients With Heart Failure

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ABSTRACT

Background: The lowest minute ventilation (VE) and carbon dioxide production (VCO_2) ratio during exercise has been suggested to be the most stable and reproducible marker of ventilatory efficiency in patients with heart failure (HF). However, the prognostic power of this index is unknown.

Methods and Results: A total of 847 HF patients underwent cardiopulmonary exercise testing (CPX) and were followed for 3 years. The associations between the lowest VE/VCO_2 ratio, maximal oxygen uptake (peak VO_2), the VE/VCO_2 slope, and major events (death or transplantation) were evaluated using proportional hazards analysis; adequacy of the predictive models was assessed using Akaike information criterion (AIC) weights. There were 147 major adverse events. In multivariate analysis, the lowest VE/VCO_2 ratio (higher ratio associated with greater risk) was similar to the VE/VCO_2 slope in predicting risk (hazard ratios [HR] per unit increment 2.0, 95% CI 1.1−3.4, and 2.2, 95% CI 1.3−3.7, respectively; $P < .01$), followed by peak VO_2 (HR 1.6, 95% CI 1.1−2.4, $P = .01$). Patients exhibiting abnormalities for all 3 responses had an 11.6-fold higher risk. The AIC weight for the 3 variables combined (0.94) was higher than any single response or any combination of 2. The model including all 3 responses remained the most powerful after adjustment for β-blocker use, type of HF, and after applying different cut points for high risk.

Conclusions: The lowest VE/VCO_2 ratio adds to the prognostic power of conventional CPX responses in HF. (*J Cardiac Fail 2009;15:756−762*)

Key Words: Exercise testing, oxygen uptake, outcomes.

Cardiopulmonary exercise testing (CPX) has been widely used the last 2 decades to quantify functional limitations and estimate risk for adverse outcomes in patients with chronic heart failure (HF). Maximal oxygen uptake (peak VO_2) is considered the gold standard for quantifying an individual's cardiopulmonary limits, and numerous studies have demonstrated the prognostic utility of this measurement.[1] In recent years however, a great deal of interest has arisen regarding other CPX markers of risk; these have largely focused on indices of ventilatory inefficiency. For example, over the last decade, the VE/VCO_2 slope, expressed as the slope of the linear relation between minute ventilation (VE) and carbon dioxide production (VCO_2), has been demonstrated to be a more powerful predictor of risk for mortality, hospitalization, and other outcomes than peak VO_2.[1−5] There have also been other expressions of ventilatory inefficiency associated with poor outcomes in HF, including the oxygen uptake efficiency slope,[6] VO_2 kinetics,[7] end-tidal CO_2 pressure at rest and during exercise,[8,9] VO_2 in recovery from exercise,[10] and oscillatory ventilation.[11] These indices have been shown to predict risk independently and to complement peak VO_2 in estimating prognosis in patients with HF.[1]

Although indices of ventilatory inefficiency and their association with outcomes in HF have been the topic of a great deal of recent investigation, the optimal multivariate application of these responses for estimating prognosis has not been established. Sun and colleagues[12] recently studied the influence of age, gender, body size, fitness, testing site, and exercise mode on ventilatory efficiency in 474 healthy

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adults. They observed that, relative to other indices of ventilatory inefficiency, the lowest VE/VCO_2 ratio during exercise was the most reproducible and stable response across laboratory sites, exercise mode, gender, and age. They concluded that the lowest VE/VCO_2 ratio represented the preferred noninvasive index to estimate ventilatory inefficiency. Although the VE/VCO_2 slope has become well-established as a marker of prognosis in recent years,[1–5] it has been suggested that the VE/VCO_2 ratio may be a more stable marker of ventilatory inefficiency because the VE/VCO_2 slope is subject to transient hyperventilation early in exercise (from anxiety) and is affected by metabolic acidosis during high levels of exercise.[12] Given the suggestion that it is a more stable marker of ventilatory efficiency, it would be useful to determine the prognostic utility of the VE/VCO_2 ratio in patients with HF. To our knowledge, the prognostic value of this index has not been studied. In the current study, we evaluated this index along with the well-established indices of risk, peak VO_2, and the VE/VCO_2 slope, and their association with outcomes in a group of patients with stable HF.

Methods

This study was a multicenter, retrospective analysis including HF patients from the exercise laboratories at the VA Palo Alto Health Care System, Palo Alto, California; San Paolo Hospital, Milan, Italy; Virginia Commonwealth University, Richmond, Virginia; Wake Forrest University Baptist Medical Center, Winston-Salem, North Carolina; and the LeBauer Cardiovascular Research Foundation, Greensboro, North Carolina. A total of 847 consecutive patients with stable chronic HF, tested between March 18, 1993, and November 15, 2007, were included. Subjects received routine follow-up care, and all surviving patients were followed for a minimum of 3 years. Inclusion criteria consisted of a diagnosis of HF[13] and evidence of left ventricular systolic (ejection fraction <40%) or diastolic dysfunction by 2-dimensional echocardiography obtained within 1 month of exercise testing. Systolic dysfunction was present in 81.3% of the sample. Subjects received routine follow-up care at the 4 institutions included in the study. All subjects completed a written informed consent and institutional review board approval was obtained at each institution.

CPX Procedure and Data Collection

Symptom-limited CPX was performed on all patients using treadmill or cycle ergometer ramping protocols.[14] A treadmill was used for testing in the American centers, whereas a cycle ergometer was used in the European center. We previously observed that optimal peak VO_2 and VE/VCO_2 slope threshold values for estimating prognosis were similar irrespective of mode of exercise in patients with HF.[15] Ventilatory expired gas analysis was performed using a metabolic cart at all 4 centers (Medgraphics CPX-D or ULTIMA PFX, Minneapolis, MN; ORCA Diagnostics, Santa Barbara, CA; Parvo Medics TrueOne 2400, Sandy, UT; or Sensormedics Vmax29, Yorba Linda, CA). Before each test, the equipment was calibrated in a standard fashion using reference gases. A standard 12-lead electrocardiogram was 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 and pressure, saturated), oxygen uptake (VO_2, standard temperature and pressure, dry), carbon dioxide production (VCO_2, standard temperature and pressure, dry) and other CPX variables were acquired breath-by-breath and averaged over 10- or 15-second intervals. Peak VO_2 and peak respiratory exchange ratio were expressed as the highest averaged samples obtained during the exercise test. VE and VCO_2 responses throughout exercise were used to calculate the VE/VCO_2 slope via least squares linear regression ($y = mx + b$, $m =$ slope). Previous work by our group and others has shown this method of calculating the VE/VCO_2 slope to be optimal for estimating prognosis.[16,17] The ratio of VE to VCO_2 was calculated each minute during exercise; the lowest minute sample was taken as the lowest VE/VCO_2 ratio.

Endpoints

A composite variable including total mortality and cardiac transplantation was the primary endpoint. Left ventricular assist device implantation was considered as a component of the composite end point, but no left ventricular assist device implantations occurred during the 3-year follow-up period. All survivors were followed for a minimum of 3 years. Ninety-seven percent of the outcomes were total mortality. The most common causes of mortality, as per discharge diagnosis, were sudden cardiac death (45%) and worsening HF (55%). Subjects were followed for major cardiac-related events after their exercise test using the Social Security Death Index and hospital and outpatient medical chart review. Follow-up was performed by the HF program at each respective institution, providing a high likelihood that all major events were captured. Clinicians conducting the CPX were not involved in decisions regarding cause of death or heart transplant/left ventricular assist device implantation.

Statistical Analysis

NCSS software (Kayesville, UT) was used to perform unpaired *t*-tests for comparisons of continuous variables and chi-square tests to compare categorical variables between those who achieved above versus below each CPX threshold. Receiver operating characteristic (ROC) curve analysis, using the composite end point at 3 years, was used to define optimal threshold values for each CPX response. Optimal thresholds were chosen using the ‘‘shortest distance to one’’ criterion on the ROC curve.[18] Z-tests were used to assess whether each ROC curve differed from chance for each of the CPX responses. Optimal thresholds for abnormal for each of the CPX variables were as follows: VE/VCO_2 slope ($\geq$34), peak VO_2 (<14 mL·kg·min), and lowest VE/VCO_2 ratio ($\geq$33). Cox proportional hazards analysis was used to determine age- and CPX- (VE/VCO_2 slope, peak VO_2, and lowest VE/VCO_2 ratio) adjusted hazard ratios for the variables included in the model; each expressed dichotomously using the threshold value. The proportional hazard assumptions were confirmed for each variable using the scaled Schoenfeld residual. The linearity of the relation between abnormal responses for peak VO_2, the VE/VCO_2 slope, and the lowest VE/VCO_2 ratio was confirmed by plotting each response against mortality. The Akaike Information Criterion (AIC) method was used to compare the predictive accuracy of the models.[19] The AIC and proportional hazards analyses were repeated using different cut points for high risk and after adjustment for β-blocker use.

Table 1. Mean Values for Demographic, Clinical, and Exercise Test Data, and Associated Univariate Hazard Ratios for Death or Transplantation through 3 Years

	Mean ± SD	Hazard Ratio (95% CI)	*P* Value
Demographic characteristics			
Age (y)	57 ± 14	1.01 (0.99−1.02)	.22
Height (cm)	171 ± 10	1.01 (0.99−1.03)	.48
Weight (kg)	84 ± 20	0.98 (0.97−0.99)	<.001
Body mass index (kg/m^2)	28.4 ± 5.9	0.93 (0.90−0.97)	<.001
Clinical characteristics (%)			
LVEF	32.1 ± 14.1	0.96 (0.95−0.98)	<.001
β-blocker	66.6	0.69 (0.47−1.02)	.06
ACE inhibitor	73.6	1.4 (0.91−2.17)	.12
Diuretic	80.8	1.7 (0.89−3.21)	.10
Aldosterone antagonist	27.6	1.22 (0.80−1.88)	.35
Exercise test responses			
Maximal heart rate (beats/min^{-1})	127 ± 21	0.98 (0.97−0.99)	<.001
Maximal SBP (mm Hg)	154 ± 38	0.99 (0.98−1.00)	.09
Peak VO_2 (mL·kg·min)	15.1 ± 4.9	0.89 (0.89−0.93)	<.0001
% age-predicted peak VO_2	59.7 ± 19	0.97 (0.97−0.98)	<.0001
Lowest VE/VCO_2 ratio	35.2 ± 7.6	1.06 (1.04−1.08)	<.0001
VE/VCO_2 slope	35.7 ± 8.3	1.07 (1.05−1.08)	<.0001
Maximal RER	1.08 ± 0.12	1.52 (0.32−7.10)	.60

All variables except medications are expressed continuously; hazard ratios for all variables except medications are for a 1-unit increase.
LVEF, left ventricular ejection fraction; ACE, angiotensin-converting enzyme; SBP, systolic blood pressure; VE/VCO_2, minute ventilation and carbon dioxide production; RER, respiratory exchange ratio.

Results

The study sample comprised 602 males and 245 females with HF; 331 (39%) had an ischemic etiology. Table 1 shows the mean demographic data, exercise test responses, and univariate hazard ratios using continuous data for the study group. The mean age of the cohort was 57 ± 14 years and the mean body mass index was 28.4 ± 5.9 kg/m^2. The key exercise test responses, including peak heart rate, peak VO_2, peak VO_2 as a percentage of age-predicted, the VE/VCO_2 slope, and the lowest VE/VCO_2 ratio all yielded significant hazard ratios.

There were 147 events (143 deaths and 4 transplantations) over the follow-up period. Areas under the ROC curves and optimal thresholds for peak VO_2, the VE/VCO_2 slope, and lowest VE/VCO_2 ratio are presented in Table 2. The optimal thresholds for peak VO_2, the VE/VCO_2 slope, and lowest VE/VCO_2 ratio were $</\geq 14$ mL·kg·min, $</\geq 34$, and $</\geq 33$, respectively. A Kaplan-Meier survival curve illustrating patients achieving <33 and ≥ 33 for the lowest VE/VCO_2 ratio is shown in Fig. 1; those with a lowest VE/VCO_2 ratio ≥ 33 had a significantly higher mortality than those with a value <33. Demographic data and exercise test responses among patients achieving below and above the optimal threshold values for the lowest VE/VCO_2 ratio, the VE/VCO_2 slope, and peak VO_2 are shown in Table 3. Peak VO_2 and maximal heart rate were significantly lower; the lowest VE/VCO_2 ratio and VE/VCO_2 slope were significantly higher among patients achieving an abnormal value for each response.

Using the optimal thresholds, the lowest VE/VCO_2 ratio and the VE/VCO_2 slope had similar prognostic power by univariate analysis (hazard ratios [HR] 3.45, 95% CI 2.1−5.6, and 3.45, 95% CI 2.2−5.6, respectively, $P < .001$), followed by peak VO_2 (HR 2.1, 95% CI 1.4−3.1, $P < .001$). By age-adjusted multivariate analysis, the respective HRs were 2.0 (95% CI 1.1−3.4, $P = .02$), 2.2 (95% CI 1.3−3.7, $P = .002$), and 1.6 (1.1−2.4, $P = .01$). These results did not change appreciably when adjusted for type of HF (systolic/diastolic dysfunction or ischemic/nonischemic). Similarly, neither the proportional hazards results nor the ROC cut points changed appreciably when patients taking β-blockers were analyzed separately or when the follow-up times were standardized to a range of time points, including 2, 3, or 4 years.

Table 4 presents age-adjusted AIC weights for models using peak VO_2, the VE/VCO_2 slope, and lowest VE/VCO_2 ratio independently and in various combinations. The model including all 3 variables had the highest predictive value (0.94, indicating a 94% probability of being the strongest model). The model including all 3 responses remained the most powerful after adjustment for beta blocker use and after applying different cut points for high risk.

Table 2. AUC and Optimal Thresholds for Peak VO_2, the VE/VCO_2 Slope, and Lowest VE/VCO_2 Ratio

	AUC	*P* Value*	Optimal Threshold	Sensitivity	Specificity
Lowest VE/VCO_2 ratio	0.67	<.001	$</\geq 33$	79%	52%
VE/VCO_2 slope	0.68	<.001	$</\geq 34$	74%	57%
Peak VO_2	0.67	<.001	$</\geq 14$	73%	54%

AUC, area under the receiver operating characteristic curve; VE/VCO_2, minute ventilation and carbon dioxide production; peak VO_2, maximal oxygen uptake.
*AUC values did not differ from one another; *P* value refers to whether accuracy of each test differed from chance.

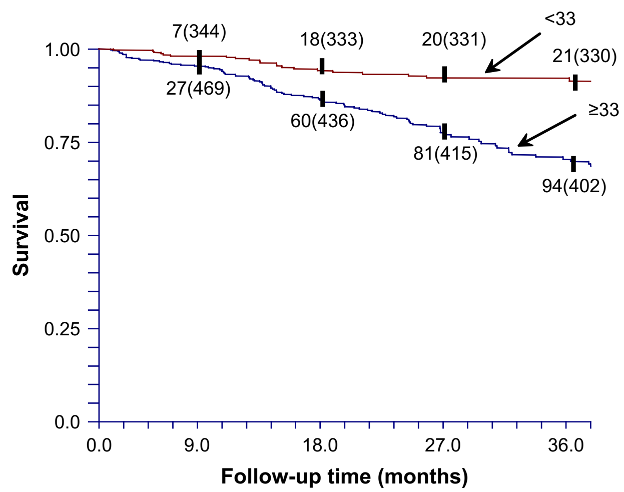

Fig. 1. Kaplan-Meier curves for patients achieving ≥33 or <33 for the lowest minute ventilation (VE) and carbon dioxide production (VCO_2) ratio ($P < .01$). Numbers given along the curves are cumulative numbers of composite outcomes; numbers in parentheses are patients evaluated at each time point.

Table 5 presents relative risks associated with abnormal peak VO_2, VE/VCO_2 slope, lowest VE/VCO_2 ratio, and their combination. Risk for an adverse event was highest when all 3 responses were abnormal. Patients exhibiting abnormalities for all 3 responses had an annual event rate of approximately 14%, and an 11.6-fold higher risk compared to patients whose responses were normal.

Discussion

The CPX has been widely applied over the last 2 decades as a tool for risk stratifying patients with HF.[1] The prognostic applications of the CPX have been expanded in recent years to include markers of ventilatory inefficiency and hemodynamic responses in addition to peak VO_2.[1–11] Most notably, the VE/VCO_2 slope has consistently been shown to be a more powerful predictor of risk than peak VO_2 in these patients.[1,3,20] Other markers of ventilatory inefficiency, such as oscillatory ventilation, the oxygen uptake efficiency slope, an early ventilatory threshold, and low resting or exercise end-tidal CO_2 pressure, have been shown to be independent prognostic markers or to complement peak VO_2 in estimating prognosis in patients with HF.[1,2,4,5,8,9,11,21] Although multivariable efforts to optimize these markers for estimating risk in HF have been the topic of numerous investigations in recent years,[1,21,22] the optimal expression of ventilatory inefficiency has not been fully explored. Because it was recently reported that the lowest VE/VCO_2 ratio during exercise (a different expression of ventilatory inefficiency than the VE/VCO_2 slope) was the most reproducible and stable response relative to other indices of ventilatory inefficiency,[12] we sought to determine its prognostic utility.

Our sample comprised a typical heterogeneous group of patients with CHF, with a mean peak VO_2 of 15.1 mL·kg·min, a mean LVEF of 32%, and with 67% of subjects taking a β-blocker. Because the prognostic power of peak VO_2 and the VE/VCO_2 slope have been well-established using conventional proportional hazards methods,[1,22] the additive predictive accuracy afforded by adding the lowest VE/VCO_2 ratio was assessed using a model selection method designed to compare multiple candidate models and determine which most accurately describes the data (the AIC weight). We observed that adding the lowest VE/VCO_2 ratio to the more established markers of prognosis (peak VO_2 and the VE/VCO_2 slope) provided the highest prediction of risk for

Table 3. Demographic Characteristics and Exercise Test Responses for Subjects above and below the Threshold Values for Lowest VE/VCO_2 Ratio, VE/VCO_2 Slope, and Peak VO_2

	Lowest VE/VCO_2 Ratio			VE/VCO_2 Slope			Peak VO_2 (mL·kg·min)		
	<33	≥33	P Value	<34	≥34	P Value	<14	≥14	P Value
Demographic characteristics	(n = 351)	(n = 496)		(n = 413)	(n = 434)		(n = 382)	(n = 465)	
Age (y)	55 ± 13	59 ± 14	<.001	54 ± 14	60 ± 13	<.001	59 ± 13	56 ± 14	<.001
Height (cm)	171.6 ± 9.8	170.7 ± 10.2	.19	172 ± 10	170 ± 9	0.2	169 ± 10	173 ± 10	<.001
Weight (kg)	87.7 ± 20.7	81.0 ± 19.8	<.001	87.8 ± 22.1	79.7 ± 18.0	<.001	83.0 ± 20.4	84.4 ± 20.5	.32
Body-mass index	29.6 ± 27.6	27.6 ± 5.8	<.001	29.5 ± 6.3	27.4 ± 5.3	<.001	29.0 ± 6.3	28.0 ± 5.6	.02
Resting values									
Heart rate (beats/min^{-1})	75 ± 12	75 ± 14	.93	75 ± 13	75 ± 14	0.86	77 ± 14	74 ± 12	.02
Blood pressure (mm Hg)									
Systolic	122 ± 28	122 ± 26	.93	124 ± 25	122 ± 26	0.56	126 ± 27	120 ± 26	.02
Diastolic	74 ± 15	72 ± 13	.32	74 ± 12	72 ± 13	0.29	74 ± 12	72 ± 15	.17
Maximal values									
Heart rate (beats/min^{-1})	134 ± 20	122 ± 21	<.001	132 ± 21	123 ± 21	<.001	118 ± 20	135 ± 19	<.001
Blood pressure (mm Hg)									
Systolic	163 ± 37	149 ± 37	<.001	163 ± 33	148 ± 37	<.001	151 ± 39	156 ± 37	.15
Diastolic	79 ± 19	76 ± 19	.17	79 ± 16	76 ± 20	.08	78 ± 18	77 ± 20	.54
Ventilatory responses									
Peak VO_2 (mL· kg^{-1}·min^{-1})	17.2 ± 5.2	13.6 ± 4.1	<.001	16.8 ± 5.2	13.4 ± 4.0	<.001	11.0 ± 2.1	18.4 ± 4.0	<.001
VE/VCO_2 slope	29.9 ± 3.9	39.7 ± 8.2	<.001	29.4 ± 3.0	41.5 ± 7.5	<.001	38.9 ± 9.4	32.9 ± 6.1	<.001
Lowest VE/VCO_2 ratio	28.9 ± 2.7	39.6 ± 6.9	<.001	30.3 ± 4.0	39.7 ± 7.5	<.001	38.3 ± 8.5	32.6 ± 5.7	<.001

Values are mean ± SD. P values are for comparisons between cut points in each group.

VE/VCO_2, minute ventilation and carbon dioxide production; peak VO_2, maximal oxygen uptake.

Table 4. Age-adjusted AIC weights for Models using Peak VO_2, VE/VCO_2 Slope, and Lowest VE/VCO_2 Ratio Separately, Paired, and Combined

	AIC Weight
Model 1 Peak $VO_2 < 14$	<0.01
Model 2 VE/VCO_2 slope ≥34	<0.01
Model 3 Lowest VE/VCO_2 ratio ≥33	<0.01
Model 4 Peak $VO_2 < 14$ VE/VCO_2 slope ≥34	0.05
Model 5 Peak $VO_2 < 14$ Lowest VE/VCO_2 ratio ≥33	<0.01
Model 6 VE/VCO_2 slope ≥34 Lowest VE/VCO_2 ratio ≥33	0.02
Model 7 Peak $VO_2 < 14$ VE/VCO_2 slope ≥34 Lowest VE/VCO_2 ratio ≥33	0.94

AIC, Akaike Information Criteria; VO_2, maximal oxygen uptake; VE/VCO_2, minute ventilation and carbon dioxide production.

the composite outcome (mortality and transplantation). Including the 3 variables together yielded a 94% probability that the model was superior; this contrasts the negligible probability when using any one of the variables alone (Table 4). It is also noteworthy that the highest risk was generated in the model that included peak VO_2, the VE/VCO_2 slope, and the lowest VE/VCO_2 ratio together (Table 5). When all 3 of the responses were abnormal, a nearly 12-fold risk of having an event was observed (Table 5). Finally, the results were not influenced by β-blocker use; the findings were similar when the models were controlled for β-blocker use or when patients not taking β-blockers were excluded (33% of the sample).

There are several clinically salient applications from the current study. The lowest VE/VCO_2 ratio is a readily available CPX response that appears to strongly predict risk in HF, and one that complements the conventional markers of risk: peak VO_2 and the VE/VCO_2 slope. The lowest VE/VCO_2 ratio has been suggested to be the preferred noninvasive index of ventilatory efficiency based on its low variability, high reproducibility, and stability across centers and exercise modes.[12] The lowest VE/VCO_2 ratio will occur at or just below the ventilatory threshold[12,23] and is therefore less influenced by the variation that accompanies hyperventilation at higher levels of exercise. Given the growing awareness of the need to apply statistical techniques to develop evidence-based multivariable approaches for improving clinical decision-making,[24] the application of the 3 CPX responses used in the current study would appear to optimize the estimation of risk in patients with HF; each provided independent risk information, and the AIC model that included all 3 variables (Table 5) demonstrated that each response augmented the predictive power of the model.[19] It is also noteworthy that both the VE/VCO_2 slope and the lowest VE/VCO_2 ratio were stronger predictors of risk than peak VO_2,

Table 5. Hazard Ratios for Death and Transplantation Associated with Abnormal Peak VO_2, VE/VCO_2 Slope, Lowest VE/VCO_2 Ratio, and their Combination*

Exercise Test Response	Description	Hazard Ratio	95% CI	*P* Value	% Event free (95% CI)
Peak VO_2 (mL·kg·min) ≥14 VE/VCO_2 slope <34 Lowest VE/VCO_2 < 33	All responses normal (n = 218; number of events = 9)	1 (reference)	—	—	96 (92–99)
Peak VO_2 (mL·kg·min) ≥14 VE/VCO_2 slope <34 Lowest VE/VCO_2 ≥ 33	Lowest VE/VCO_2 ratio abnormal only (n = 56; number of events = 11)	3.08	1.03–9.17	.04	80 (64–96)
Peak VO_2 (mL·kg·min) ≥14 VE/VCO_2 slope ≥34 Lowest VE/VCO_2 < 33	VE/VCO_2 slope abnormal only (n = 32; number of events = 6)	4.94	1.44–16.98	<.001	80 (61–99)
Peak VO_2 (mL·kg·min) <14 and VE/VCO_2 slope <34 and Lowest VE/VCO_2 < 33	Peak VO_2 abnormal only (n = 77; number of events = 12)	3.25	1.17–8.99	.02	85 (76–95)
Peak VO_2 (mL·kg·min) <14 and VE/VCO_2 slope ≥34 and Lowest VE/VCO_2 < 33	Peak VO_2 and VE/VCO_2 slope abnormal (n = 29; #events = 6)	5.30	1.55–18.14	.008	81 (64–98)
Peak VO_2 (mL·kg·min) < 14 and VE/VCO_2 slope <34 and Lowest VE/VCO_2 ≥ 33	Peak VO_2 and lowest VE/VCO_2 ratio abnormal (n = 53; #events = 15)	5.52	2.10 – 14.50	<.001	72 (57–88)
Peak VO_2 (mL·kg·min) ≥14 and VE/VCO_2 slope ≥34 and Lowest VE/VCO_2 ≥ 33	VE/VCO_2 slope and lowest VE/VCO_2 ratio abnormal (n = 154; number of events = 52)	7.10	3.11 – 16.21	<.001	66 (56–77)
Peak VO_2 (mL·kg·min) < 14 and VE/VCO_2 slope ≥34 and Lowest VE/VCO_2 ≥ 33	All 3 abnormal (n = 228; number of events = 96)	11.62	5.28 – 25.57	<.001	58 (49–67)

VE/VCO_2, minute ventilation and carbon dioxide production; peak VO_2, maximal oxygen uptake.
*Adjusted for age and for one another.

reinforcing the concept emphasized in recent studies and guidelines that measures of ventilatory inefficiency should be included in the risk paradigm when evaluating patients with HF.[1,21,22,25]

The VE/VCO_2 ratio (commonly termed the *ventilatory equivalent for CO_2*) differs from the index that has been widely used to estimate risk in recent years, the VE/VCO_2 slope, in that it is derived at a single time point during exercise. In accordance with the alveolar gas equation, a heightened VE/VCO_2 ratio may occur due to a low partial pressure of arterial carbon dioxide, an abnormally high dead space fraction of tidal volume, or both. In patients with HF, partial pressure of arterial carbon dioxide changes only slightly during exercise[26]; therefore, a heightened VE/VCO_2 ratio is likely due to a high dead space ventilation (high dead space fraction of tidal volume) from poor perfusion of ventilated alveoli. One of the hallmarks of HF is an impaired cardiac output response to exercise,[27] which underlies the mismatching between ventilation and perfusion in the lungs (and therefore a heightened dead space fraction of tidal volume). Thus, a higher VE/VCO_2 ratio will reflect a more impaired cardiac output response to exercise. Although the prognostic value of the lowest VE/VCO_2 ratio has not been studied to our knowledge, several studies have addressed the prognostic utility of the *peak* VE/VCO_2 ratio in patients with HF. Arena and colleagues[28] reported that the VE/VCO_2 slope and the peak exercise VE/VCO_2 ratio provided similar prognostic power in terms of predicting mortality or hospitalization in patients with HF (ROC curves 0.87 and 0.85 for the VE/VCO_2 slope and ratio, respectively). Mejhert et al[29] reported that the peak VE/VCO_2 ratio was a stronger predictor of mortality than peak VO_2 and the VE/VCO_2 slope; patients with a heightened peak VE/VCO_2 ratio had a nearly 7-fold higher risk of mortality. Using the VE/VCO_2 ratio at the anaerobic threshold (analogous to the *lowest* VE/VCO_2 ratio), MacGowan and colleagues[30] observed that an abnormal response (>50) provided prognostic information that complemented peak VO_2; 82% of patients with a VE/VCO_2 ratio at the anaerobic threshold >50 and a peak $VO_2 \leq 15$ mL·kg·min died during a mean follow-up of 552 days. Robbins et al[31] reported that the VE/VCO_2 ratio at the anaerobic threshold was similar to the peak VE/VCO_2 ratio in predicting mortality.

Limitations

Our study was limited by the fact that the sample was predominately male with moderate disease. As with any approach, the findings must be validated in different populations of patients with HF. In addition, there has recently been a variety of CPX variables related to ventilatory inefficiency that have been applied for the purposes of predicting outcomes in HF (eg, oscillatory ventilation, end-tidal CO_2 pressure, VO_2 kinetics during exercise, VO_2 in recovery)[1]; the role that the lowest VE/VCO_2 ratio plays in supplementing these indices requires further exploration.

Summary

The lowest VE/VCO_2 ratio during exercise is a powerful marker of prognosis in patients with HF, and provides prognostic information that is independent from peak VO_2 and the VE/VCO_2 slope. The lowest VE/VCO_2 ratio complements peak VO_2 and the VE/VCO_2 slope when estimating risk in patients with HF and should be considered when performing CPX to determine prognosis.

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