Imaging and Diagnostic Testing

Peak VO_2 and VE/VCO_2 slope in patients with heart failure: A prognostic comparison

Ross Arena, PhD, PT,[a] Jonathan Myers, PhD,[b] Syed Salman Aslam, MD,[b] Elsa B. Varughese, MD,[b] and Mary Ann Peberdy, MD, FACC[a] ***Richmond, Va, and Palo Alto, Calif***

Background Exercise testing with ventilatory expired gas analysis has proven to be a valuable tool for assessing patients with heart failure (HF). Peak oxygen consumption (peak VO_2) continues to be considered the gold standard for assessing prognosis in HF. The minute ventilation – carbon dioxide production relationship (VE/VCO_2 slope) has recently demonstrated prognostic significance in patients with HF, and in some studies, it has outperformed peak VO_2.

Methods Two hundred thirteen subjects, in whom HF was diagnosed, underwent exercise testing between April 1, 1993, and October 19, 2001. The ability of peak VO_2 and VE/VCO_2 slope to predict cardiac-related mortality and hospitalization was examined.

Results Peak VO_2 and VE/VCO_2 slope were demonstrated with univariate Cox regression analysis both to be significant predictors of cardiac-related mortality and hospitalization ($P < .01$). Multivariate analysis revealed that peak VO_2 added additional value to the VE/VCO_2 slope in predicting cardiac-related hospitalization, but not cardiac mortality. The VE/VCO_2 slope was demonstrated with receiver operating characteristic curve analysis to be significantly better than peak VO_2 in predicting cardiac-related mortality ($P < .05$). Although area under the receiver operating characteristic curve for the VE/VCO_2 slope was greater than peak VO_2 in predicting cardiac-related hospitalization (0.77 vs 0.73), the difference was not statistically significant ($P = .14$).

Conclusions These results add to the present body of knowledge supporting the use of cardiopulmonary exercise testing in HF. Consideration should be given to revising clinical guidelines to reflect the prognostic importance of the VE/ VCO_2 slope in addition to peak VO_2. (Am Heart J 2004;147:354–60.)

The prognostic value of exercise testing in the heart failure (HF) population is well established. Peak oxygen consumption (VO_2) has consistently demonstrated prognostic significanc[1-3] and is the most frequently analyzed cardiopulmonary exercise test parameter.[4] In conjunction with other typically more invasive evaluation techniques, peak VO_2 is used to assess survival and the need for heart transplantation.[4] Other ventilatory expired gas parameters obtained during exercise testing have recently demonstrated prognostic value. Because of the wealth of information exercise testing provides, exploration into the prognostic usefulness of additional parameters is warranted.

The relationship between minute ventilation and carbon dioxide production (VE/VCO_2 slope) is one such cardiopulmonary exercise test parameter that appears to have clinical value. The VE/VCO_2 slope is elevated in most patients with HF.[5-7] This elevated VE/VCO_2 slope is inversely related to cardiac output at peak exercise[5] and is at least partly explained by a decrease in pulmonary perfusion.[6,7] Because of its association with cardiac function, the prognostic value the VE/VCO_2 slope consistently demonstrates is not surprising.[3,8-13] The VE/VCO_2 slope may also be a better predictor of outcome than peak VO_2 in the HF population.[3,8,10,11,14] With Cox multivariate analysis, the VE/VCO_2 slope has outperformed peak VO_2 in predicting mortality[3,10,11,14] and, more recently, hospitalization.[8] To date however, differences in the prognostic power between peak VO_2 and the VE/VCO_2 slope have not been widely emphasized, and the former remains the most fre-

From the [a]Department of Physical Therapy, Virginia Commonwealth University Medical Center, Richmond, Va, and [b]VA Palo Alto Health Care System, Cardiology Division, Stanford University, Palo Alto, Calif.
Submitted October 28, 2002; accepted July 18, 2003.
Reprint requests: Ross Arena, PhD, PT, Assistant Professor, Department of Physical Therapy, Box 980224, Virginia Commonwealth University, Medical College of Virginia Health Sciences Campus, Richmond, VA 23298-0224.
E-mail: raarena@vcu.edu
0002-8703/$ - see front matter

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quently assessed cardiopulmonary exercise parameter in HF. The purpose of this investigation was to compare peak VO_2 and the VE/VCO_2 slope for predicting mortality and hospitalization in patients with HF.

Methods

Two hundred thirteen subjects, assessed between April 1, 1993, and October 19, 2001, were included in the study. One hundred forty-four subjects underwent exercise testing and were subsequently observed at the Veterans Hospital in Palo Alto, Calif. The remaining 69 subjects were tested and observed in the heart failure program at the Virginia Commonwealth University Medical Center in Richmond. All subjects underwent tested on an outpatient basis. The exercise tests were conducted as part of the subjects standard of care (initial assessment or follow-up) or as part of a prior research study. Because all subjects in this study underwent tested on an outpatient basis and therefore apparently not at the end-stage of disease progression, HF severity of this group should be considered mild-moderate. Regardless of the reason for testing, procedures for the exercise protocol and mode, monitoring, and data collection were consistent in the data set. Written informed consent was obtained from all subjects before testing. Approval from the appropriate institutional review board was obtained for those subjects undergoing an exercise test as part of a prospective research project. Subject and pharmacological characteristics are listed in Table I.

Inclusion criteria consisted of a diagnosis of HF and evidence of systolic dysfunction by means of an echocardiogram or cardiac catheterization. Twenty-two subjects were excluded because the mechanism of HF was attributed to diastolic dysfunction. No subjects were excluded because of a primary diagnosis of obstructive/restrictive pulmonary disease. Ten subjects who received their regular or emergent care at a facility other than those aforementioned were also excluded. The latter exclusion criteria helped ensure end points of interest were not missed. This sample is considered to be a consecutive series of subjects in the specified period whose data were included in the analysis provided the inclusion criteria were met. Selection bias was therefore not a concern at either center. All patients, from both centers, with a diagnosis of HF caused by systolic dysfunction and exercise test data were included in this analysis.

Table I. Subject characteristics

Number of subjects (m/f)	213 (185/28)
Age (y) (mean ± SD)	57.2 ± 13.5 (range 15–86)
Left ventricular ejection fraction (mean ± SD)	30.1% ± 10.7% (range 10%–45%)
Etiology (ischemic/nonischemic)	117*/96†
ACE inhibitor	149
Cardiac glycoside	122
Diuretic	134
Nitrate	62
β-Blocker	89
Calcium-channel blocker	32
Anticoagulant	75
Antiarrhythmic	33

Values given as number of subjects unless otherwise indicated.
*A total of 117 subjects had a history of coronary artery disease (as evidenced by cardiac catheterization) and myocardial infarction.
†A total of 96 subjects did not have a history of coronary artery disease (as evidenced by cardiac catheterization) or myocardial infarction.

Equipment calibration

Ventilatory expired gas analysis was obtained through one of several metabolic systems depending on the clinic and time frame for exercise testing (Medgraphics CPX-D, Minneapolis, Minn; Sensormedics Vmax29, Yorba Linda, Calif; Schiller CS-100, Baar, Switzerland; and Orca Diagnostics, Santa Barbara, Calif). The oxygen and carbon dioxide sensors were calibrated using gases with known oxygen, nitrogen, and carbon dioxide concentrations before each test. The flow sensor was also calibrated before each test.

Testing procedure and data collection

Symptom-limited exercise testing with ventilatory expired gas analysis was conducted with a treadmill or cycle ergometer. The treadmill was the only mode of exercise used at the Virginia Commonwealth University Medical Center Hospital. The Veterans Affairs Hospital likewise used a treadmill in most (approximately 90%) exercise tests. The mode of exercise was dependent on equipment availability as opposed to subject characteristics. Furthermore, there is no hypothetical rational to support the possibility that the relationship between VE and VCO_2 is dependent on exercise mode in a given subject. Both centers solely use ramping protocols for exercise testing in the HF population, which were similar in stage time and incremental workload adjustments. Monitoring consisted of continuous electrocardiography, manual blood pressure measurements, heart rate recordings every stage via the electrocardiogram, and rating of perceived exertion (Borg 6–20 scale) at each stage. Test termination criteria followed ACSM guidelines.[5]

VO_2 (mL $\times$ kg^{-1} $\times$ min^{-1}), VCO_2 (L/min), and VE (L/min) were collected throughout the exercise test. All 213 subjects had these parameters, averaged for 10-second intervals, either in hard copy or computerized format. Peak VO_2 was expressed as the highest 30-second average value obtained during the last stage of the exercise test. Ten-second averaged VE and VCO_2 data were input into spreadsheet software (Microsoft Excel, Microsoft Corp, Bellevue, Wash) as time-down columns from the start of exercise to peak. VE and VCO_2 were designated the y- and x-axis variables, respectively. VE/VCO_2 slope was calculated with the slope calculation option of the spreadsheet software package.

End points

Subjects were observed for cardiac-related mortality and hospitalization 1-year after exercise testing via medical chart review and the Social Security Death Index. Cardiac-related mortality was also separately tracked without a 1-year time constraint. Cardiac-related mortality was defined as death directly resulting from failure of the cardiac system. An example fitting this definition is myocardial infarction followed by cardiac arrest. Cardiac-related hospitalization was defined as a hospital admission directly resulting from cardiac dysfunction

Table II. Univariate Cox regression results for peak VO_2 and VE/VCO_2 slope

Predictor variable	Event	Number of events	χ^2	*P*
VE/VCO_2 slope	Cardiac mortality (1 y)	15	31.4	<.001
	Cardiac hospitalization (1 y)	61	52.7	<.001
	Cardiac mortality (overall)	33	42.4	<.001
Peak VO_2	Cardiac mortality (1 y)	15	10.6	.001
	Cardiac hospitalization (1 y)	61	29.8	<.001
	Cardiac mortality (overall)	33	9.9	.002

Table III. ROC curve analysis for the peak VO_2 and VE/VCO_2 slope classifications

Classification	Event	Number of events	Area under the ROC curve	*P*
Peak VO_2	Cardiac mortality (1 y)	15	0.78	<.001
	Cardiac hospitalization (1 y)	61	0.73	<.001
	Cardiac mortality (overall)	33	0.66	.003
VE/VCO_2 slope	Cardiac mortality (1 y)	15	0.86	<.001
	Cardiac hospitalization (1 y)	61	0.77	<.001
	Cardiac mortality (overall)	33	0.82	<.001

requiring inpatient care to correct. An example fitting this definition is decompensated HF requiring the use of an intravenous inotropic agent. Any death or hospital admission with a cardiac-related discharge diagnosis, confirmed wiht diagnostic tests or autopsy, was considered to be an event. The most common causes of mortality, as per discharge diagnosis, were cardiac arrest, myocardial infarction, and HF. The most common causes of hospitalization were decompensated HF and coronary artery disease. Subjects in whom mortality or hospitalization was of a non-cardiac etiology were treated as censored cases.

Statistical analysis

Univariate Cox regression analysis was used to determine the ability of peak VO_2 and VE/VCO_2 slope to predict 1-year cardiac-related hospitalization, 1-year cardiac-related mortality, and overall cardiac-related mortality.

Multivariate Cox regression analysis (forward stepwise method), with peak VO_2 and VE/VCO_2 slope, was used to assess the combined effect of these variables in predicting the aforementioned end points. Entry and removal *P* values for the multivariate analyses were set at .05 and .10, respectively.

Receiver operating characteristic (ROC) curves were constructed for the peak VO_2 and VE/VCO_2 slope classification schemes for the 3 end points. A z test compared the effectiveness of peak VO_2 and VE/VCO_2 slope in predicting the end points of interest.[16] Optimal threshold values (highest combination of sensitivity/specificity) were identified for the 1-year end points via ROC curve analysis. One threshold value was determined for predicting a given end point when the z test revealed a significant difference in area under the ROC curve between peak VO_2 and VE/VCO_2 slope and multivariate Cox regression analysis only retained that parameter. Two threshold values were determined for predicting a given end point when the z test revealed that the area under the ROC curves between the peak VO_2 and VE/VCO_2 slope were not significantly different and multivariate Cox regression analysis retained both parameters. A Kaplan Meier analysis and hazard ratio calculation was subsequently performed with the threshold values.

All data are reported as mean values plus or minus SD. Statistical tests with a *P* value <.05 were considered to be significant.

Results

The mean follow-up period was 32 ± 26 months, and the annual mortality rate was 5.4%. Mean values for peak VO_2 and VE/VCO_2 slope were 16.3 ± 6.0 mL $\times$ kg^{-1} $\times$ min^{-1} and 33.2 ± 7.9 mL $\times$ kg^{-1} $\times$ min^{-1}, respectively. On the basis of individual peak VO_2 values, the Weber classification for the group was: Weber class A, 51; Weber class B, 47; Weber class C, 89; Weber class D, 26. There were 15 cardiac-related deaths and 61 cardiac-related hospitalizations within 1-year after exercise testing. Overall, there were 33 cardiac-related deaths during the follow-up period, which ranged from 1.0 month to 9.2 years.

With univariate Cox regression analysis, both peak VO_2 and VE/VCO_2 slope were revealed to be significant predictors of all 3 outcomes assessed (Table II). Peak VO_2 was revealed by multivariate Cox regression analysis to add significantly to the VE/VCO_2 slope in predicting 1-year cardiac-related hospitalization (residual $\chi^2 = 6.5$; $P = .01$). The addition of peak VO_2 did not provide additional value to the VE/VCO_2 slope in predicting overall cardiac-related mortality (residual $\chi^2 = 0.2$; $P = .89$) or 1-year cardiac-related mortality (residual χ^2, 1.5; $P = .29$).

ROC curve analysis results for the peak VO_2 and VE/VCO_2 slope classifications are listed in Table III. The area under the ROC curve was greater for all VE/VCO_2 slope classification schemes than for peak VO_2. The difference in ROC area between peak VO_2 and VE/VCO_2 slope for 1-year cardiac-related hospitalization was revealed with a z test to be not statistically significant (z = 1.1; $P = .14$). However, the difference between peak VO_2 and VE/VCO_2 slope was statistically significant for overall cardiac-related mortality (z = 3.8; $P = .00007$) and 1-year cardiac-related mortality (z = 1.7; $P = .04$). A VE/VCO_2 slope cutoff ≥34 for 1-year cardiac-related hospitalization produced sensitivity and specificity rates of 73% and 67%, respectively.

A peak VO_2 cutoff $\leq$14 mL $\times$ kg^{-1} $\times$ min^{-1} for 1-year cardiac-related hospitalization produced sensitivity and specificity rates of 70% and 64%, respectively. Combining the VE/VCO_2 slope cutoff $\geq$34 (first criteria) and peak VO_2 cutoff 14 mL $\times$ kg^{-1} $\times$ min^{-1} (second criteria) for 1-year cardiac-related hospitalization produced sensitivity and specificity values of 84% and 48%, respectively. A VE/VCO_2 slope cutoff $\geq$34 for 1-year cardiac-related mortality produced sensitivity and specificity values of 66% and 93%, respectively.

The Kaplan Meier analysis for 1-year cardiac-related mortality and hospitalization with a VE/VCO_2 slope threshold of 34 is illustrated in Figure 1.

Kaplan Meier analysis for 1-year cardiac-related hospitalization with a combined VE/VCO_2 slope cutoff >34 (first criteria) and peak VO_2 cutoff $\leq$14 mL $\times$ kg^{-1} $\times$ min^{-1} (second criteria) is illustrated in Figure 2.

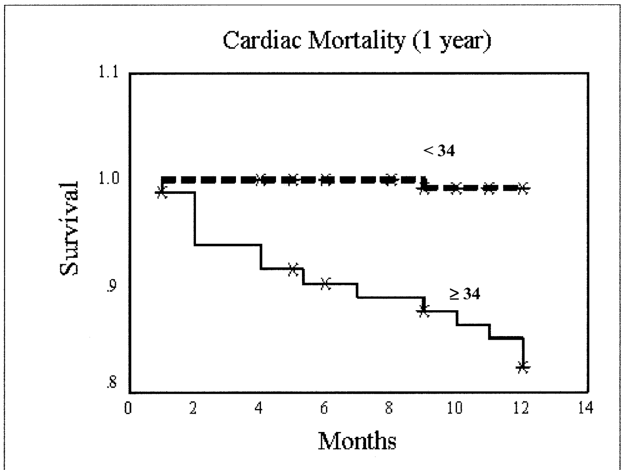
VE/VCO_2 slope, peak VO_2, and combined threshold value hazard ratios for 1-year cardiac-related mortality and hospitalization are listed in Table IV.

Discussion

The results of this study add to a growing body of data demonstrating the prognostic value of peak VO_2 and VE/VCO_2 slope in the HF population.[3,8-13] More importantly, these results support the concept that the VE/VCO_2 slope is prognostically superior to peak VO_2, an observation made recently by other investigators, although not overly emphasized.[3,8,10,11,14]

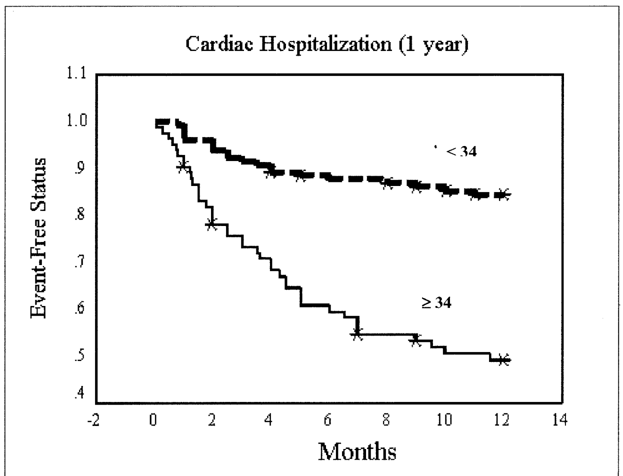
There may be several reasons for the differences between the prognostic value of the VE/VCO_2 slope and peak VO_2. Peak VO_2 has 2 potential limitations when assessing prognosis. First, a true assessment of peak VO_2 is dependent on subject effort. Even with the most diligent efforts by clinicians to illicit maximal effort, a percentage of patients with HF will voluntarily terminate the exercise test prematurely. A second potential limitation is the contribution peripheral metabolism has on peak VO_2. This contribution is made apparent with investigations demonstrating that high values for peak VO_2 are paralleled by superior skeletal muscle metabolic capacity.[17,18] 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. Thus, 2 patients with HF who have similar cardiac but differing skeletal muscle function and 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[19] who reported that among 64 patients who were examined for heart transplantation, cardiac output, and pulmonary wedge pressure responses to exercise differed markedly, despite

Figure 1



	Subjects	Deaths	Percent Survival
VE/VCO_2 slope < 34	130	1	99.2%
VE/VCO_2 slope ≥ 34	83	14	83.1%

A

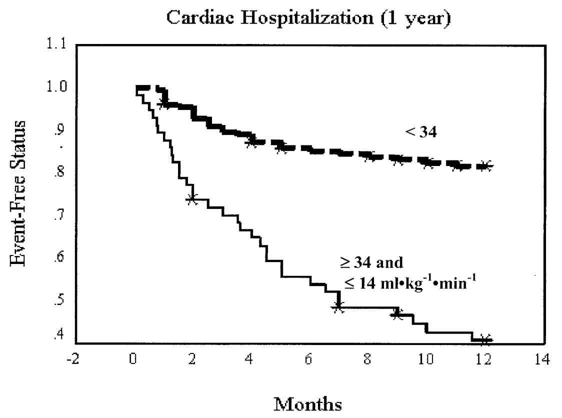


	Subjects	Cardiac Hospitalizations	Percent Survival
VE/VCO_2 slope < 34	130	20	84.6%
VE/VCO_2 slope ≥ 34	83	41	50.6%

B

A, Kaplan Meier analysis for 1-year cardiac-related mortality with VE/VCO_2 slope threshold of 34. Log rank = 20.6. $P < .0001$. **B,** Kaplan Meier analysis for 1-year cardiac-related hospitalization with VE/VCO_2 slope threshold of 34. Log rank = 31.7. $P < .0001$. *Censored cases.

Figure 2



	Subjects	Cardiac Hospitalizations	Percent Survival
VE/VCO_2 slope < 34	156	28	82.1%
VE/VCO_2 slope ≥ 34 and peak $VO_2 \leq 14$ ml•kg^{-1}•min^{-1}	57	33	42.1%

Kaplan Meier analysis for 1-year cardiac-related hospitalization with VE/VCO_2 slope threshold of 34 and peak VO_2 threshold of 14. VE/VCO_2 slope criteria assessed first (≥34). Only those subjects meeting both criteria were categorized as high risk. *Censored cases.

patients having similar values for peak VO_2. We are not disputing that a significant relationship between peak VO_2 and cardiac output exists. There are, however, factors, namely subject effort and peripheral function, that may negatively impact the strength of that relationship.

Unlike peak VO_2, the VE/VCO_2 slope is generally independent from subject effort. In addition, variation in the VE/VCO_2 slope appears to rely closely on central function in patients with HF. Elevated VE relative to CO_2 elimination is linked to decreased pulmonary perfusion[20-22] and cardiac output.[21,23] The closer reliance the VE/VCO_2 slope has on cardiac performance may contribute to its prognostic accuracy relative to peak VO_2.

We observed that the VE/VCO_2 slope was a significantly better predictor of both 1-year and overall cardiac-related mortality than peak VO_2, as indicated by the ROC curve analysis (Table III). Although peak VO_2 was a significant univariate predictor of mortality (Table II), it did not add additional value to the VE/VCO_2 slope with multivariate analysis. Although the area under the ROC curve was again greater for the VE/VCO_2 slope in predicting 1-year cardiac related hospitalization than for peak VO_2, the difference was not statistically significant (Table III). For predicting hospitalization, peak VO_2 did add additional value to the VE/VCO_2 slope. On the basis of these findings and the optimal threshold values we observed (Figures 1 and 2), risk stratification guidelines for patients with HF in this study are outlined in Table V.

The suggested strategies in Table V are made on the basis of previous investigations demonstrating the efficacy of optimal medical management and exercise intervention. Reindl et al[24] reported a significant reduction in the VE/VCO_2 slope and a significant increase in aerobic capacity in a group of patients with HF who responded to optimization of pharmacology. Myers et al[25] demonstrated a significant reduction in the VE/VCO_2 slope after 2 months of aerobic training in patients with HF. It is feasible that identification and efforts to reduce an abnormally high VE/VCO_2 slope via initiation/optimization of pharmacology, exercise training, or both is 1 targeted strategy that may prevent future hospitalizations and significantly reduce costs of care.

The addition of peak VO_2 in predicting hospitalization results in an increased sensitivity while sacrificing specificity. From a clinical standpoint, this sensitivity/specificity balance may be considered acceptable because the patients who are improperly classified (false positive) as being at increased risk for a cardiac-related hospitalization within a year after exercise testing would still benefit from an exercise prescription and review of medical management. Identifying the most individuals truly at risk for hospitalization (true positive) is of higher importance.

We emphasize that the outlined risk stratification guidelines in Table V should not be viewed as transferable to other HF groups because the retrospective design of this study limits application. The proposed guidelines in Table V should rather serve as a hypothetical template that, if supported by prospective investigations, should be considered for implementation into clinical practice.

Overall cardiac-related mortality without a defined period was 1 end point used in this study for consistency with previous investigations that assessed the prognostic usefulness of the VE/VCO_2 slope.[9,10,14,26] Limiting end points to a 1-year period may, however, be clinically optimal because of the fluid nature of cardiac function in the patient with HF. Because individuals with HF can shift from a stable to an uncompensated status (or vice versa) rather abruptly, limiting the follow-up period to 1 year is more clinically relevant for high-risk patients. A 1-year tracking period may strike a sufficient balance between avoiding outdated information and the economic constraints of multiple

Table IV. Hazard ratios for VE/VCO_2 slope peak VO_2 threshold values

End point	Threshold criteria	Hazard ratio	P
Cardiac mortality (1 y)	VE/VCO_2 slope ≥34	23.9	<.0001
Cardiac hospitalization (1 y)	VE/VCO_2 slope ≥34	4.1	<.0001
Cardiac hospitalization (1 y)	VE/VCO_2 slope ≥34 and peak VO_2 ≤14 $mL \cdot kg^{-1} \cdot min^{-1}$	4.3	<.0001

Table V. Proposed guidelines based upon study findings for 1-year risk based on VE/VCO_2 slope and peak VO_2 obtained during exercise testing in HF*

Variable	One year cardiac-related mortality	One year cardiac-related hospitalization
VE/VCO_2 slope <34	Low risk: Maintain medical management. Assess and alter exercise habits as appropriate.	Low risk: Maintain medical management. Assess and alter exercise habits as appropriate.
VE/VCO_2 slope ≥34	Increased risk: Assess present medical management and attempt to optimize.† Assess and alter exercise habits as appropriate.	See below
VE/VCO_2 slope ≥34 and peak VO_2 ≤ 14 $ml \cdot kg^{-1} \cdot min^{-1}$	See above	Increased risk: Assess present medical management and attempt to optimize.† Assess and alter exercise habits as appropriate.

*Guidelines presented here should be considered a hypothetical template requiring support from future prospective investigations before implementation into clinical practice.
†Is the patient on all medications proven beneficial for HF? If so, have dosages been optimized?

exercise tests. In addition, most research examining the prognostic value of cardiopulmonary exercise data do not use hospitalization as an end point. Given that HF is the primary hospital diagnostic-related group among Medicare patients,[27] analysis of measures predicting hospitalization in this population seems warranted. The ability of the VE/VCO_2 slope as a means of effectively predicting hospitalization may help identify high-risk patients, provide appropriate interventions, prevent non-fatal adverse events, and reduce health care costs.

Mancini et al[1] established the peak VO_2 threshold still widely used to assess appropriateness for transplantation listing. Since that landmark study, a well-established body of literature has been published documenting the prognostic usefulness of peak VO_2 in both transplant candidates and stable patients with HF.[1,2,4] These results should not be viewed as suggesting that peak VO_2 be discarded. Peak VO_2, depending on the end point of interest, adds predictive value to the VE/VCO_2 slope and, moreover, is an essential component of appropriate exercise prescription and activity guidelines. These data do suggest, however, that the application of cardiopulmonary exercise test data be widened to include the VE/VCO_2 slope.

Limitations

There are several limitations to this study. Not all our subjects were being considered for transplant at the time of testing. As aforementioned, HF severity for the group studied is considered mild to moderate. Therefore, the results may not be applicable to populations with more severe disease, such as transplant candidates. Future research should compare the prognostic value of the VE/VCO_2 slope to peak VO_2 in populations with more severe HF. In addition, this study was retrospective. Although our findings are in agreement with several previous investigations, prospective studies are required. Future studies should seek to determine the optimal prognostic interpretation of cardiopulmonary responses while strictly controlling exercise testing procedures and end point tracking. finally, most of the subjects in this study were men, limiting the ability of sex-based subgroup analysis. Although a hypothetical rationale to explain the potential for sex-based differences in the prognostic ability of VE/VCO_2 slope or peak VO_2 does not presently exist, future investigations with group characteristics suited to address this issue may be beneficial.

Conclusion

In conclusion, the results of this study provide further evidence that exercise testing with ventilatory expired gas analysis has value in the population with HF. Our data also suggest that the VE/VCO_2 slope has superior prognostic value compared with peak VO_2 in patients with HF. Strong consideration should be given to revising present clinical guidelines[4] to reflect the demonstrated prognostic value of the VE/VCO_2 slope.

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