Development of a Ventilatory Classification System in Patients With Heart Failure

Ross Arena, PhD, PT; Jonathan Myers, PhD; Joshua Abella, MD; Mary Ann Peberdy, MD; Daniel Bensimhon, MD; Paul Chase, MEd; Marco Guazzi, MD, PhD

Background—Ventilatory efficiency, commonly assessed by the minute ventilation (VE)–carbon dioxide production (VCO2) slope, is a powerful prognostic marker in the heart failure population. The purpose of the present study is to refine the prognostic power of the VE/VCO2 slope by developing a ventilatory class system that correlates VE/VCO2 cut points to cardiac-related events.

Methods and Results—Four hundred forty-eight subjects diagnosed with heart failure were included in this analysis. The VE/VCO2 slope was determined via cardiopulmonary exercise testing. Subjects were tracked for major cardiac events (mortality, transplantation, or left ventricular assist device implantation) for 2 years after cardiopulmonary exercise testing. There were 81 cardiac-related events (64 deaths, 10 heart transplants, and 7 left ventricular assist device implantations) during the 2-year tracking period. Receiver operating characteristic curve analysis revealed the overall VE/VCO2 slope classification scheme was significant (area under the curve: 0.78 [95% CI, 0.73 to 0.83], \( P < 0.001 \)). On the basis of test sensitivity and specificity, the following ventilatory class system was developed: (1) ventilatory class (VC) I: \( \leq 29 \); (2) VC II: 30.0 to 35.9; (3) VC III: 36.0 to 44.9; and (4) VC IV: \( \geq 45.0 \). The numbers of subjects in VCs I through IV were 144, 149, 112, and 43, respectively. Kaplan-Meier analysis revealed event-free survival for subjects in VC I, II, III, and IV was 97.2%, 85.2%, 72.3%, and 44.2%, respectively (log-rank 86.8; \( P < 0.001 \)).

Conclusions—A multiple-level classificatory system based on exercise VE/VCO2 slope stratifies the burden of risk for the entire spectrum of heart failure severity. Application of this classification is therefore proposed to improve clinical decision making in heart failure. (Circulation. 2007;115:--)

Key Words: prognosis ventilation heart failure exercise

The prognosis of patients diagnosed with heart failure (HF) remains poor despite recent advances in medical management.1 It is important that we refine our ability to accurately identify HF patients at the highest risk for morbidity and mortality and refer these patients for potential advanced therapies. Cardiopulmonary exercise testing (CPX) has become the cornerstone of risk stratification for HF patients. Peak oxygen consumption (VO2) was the first CPX variable to demonstrate prognostic value2 and is still the most frequently analyzed variable in clinical practice. More recently, several investigations have shown that ventilatory efficiency, typically expressed as the minute ventilation/carbon dioxide production (VE/VCO2) slope, is a strong prognostic marker in patients with HF.3–7 The majority of studies report the VE/VCO2 slope to be prognostically superior to peak VO2, which underscores the clinical importance of assessing ventilatory efficiency in HF patients (Table 1).

Clinical Perspective p

Furthermore, a number of studies define a VE/VCO2 slope of \( \approx 34 \) as a threshold value for predicting a poorer prognosis (Table 1).4–6 Although this dichotomous threshold has proven to be prognostically significant, the wide range of VE/VCO2 slope values observed in the HF population indicates that a multilevel classification system may better define the increasing risk of adverse events. The purpose of the present study was to evaluate the risk of adverse events using several VE/VCO2 slope classes, testing the hypothesis that a multilevel ventilatory classification system would more accurately identify subgroups at increasing risk for adverse events across the entire spectrum of clinical severity.

Methods

The present study is a multicenter analysis including HF patients from the CPX laboratories at San Paolo Hospital, Milan, Italy;
CPX Procedure and Data Collection
Symptom-limited CPX was performed on all patients with treadmill
or cycle ergometry ramping protocols. A treadmill was used for
testing in American centers, whereas a lower-extremity cycle
ergometer was used in the European center. Ventilatory expired
gas analysis was performed with a metabolic cart at all 5 centers
(MedGraphics CPX-D, Minneapolis, Minn, or SensorMedics Vmax29,
Yorba Linda, Calif). Before each test, the equipment was
 calibrated in standard fashion with reference gases. In addition, each
center routinely validated the metabolic exercise testing equipment
by exercising a healthy subject at a submaximal steady rate to verify
measured Vo2 matched estimated Vo2 from the workload. Previous
studies have demonstrated optimal peak Vo2 and VE/VCO2 slope
prognostic threshold values are similar regardless of the mode of
exercise in patients with HF. We therefore did not create subgroups
based on mode of CPX. Standard 12-lead ECGs were obtained at
rest, each minute during exercise, and for at least 5 minutes during
the recovery phase; blood pressure was measured with a standard
cuff sphygmomanometer. Minute ventilation (Ve), oxygen uptake
(Vo2), carbon dioxide output (VCO2), and other cardiopulmonary
variables were acquired on a breath-by-breath basis and averaged
over 10- or 15-second intervals. Peak Vo2 and peak respiratory
exchange ratio were expressed as the highest averaged samples
obtained during the exercise test. Ve and VCO2 values, acquired from
the initiation of exercise to peak exercise, were input into spreadsheet
software (Microsoft Excel, Microsoft Corp, Redmond, Wash) to calculate the Ve/VCO2 slope via least squares linear regression
(y = mx + b, where m = slope). Previous work by our group and others
has shown that this method of calculating the Ve/VCO2 slope is
prognostically optimal.

End Points
Subjects were followed up for major cardiac-related events for 2
years after CPX via hospital and outpatient medical chart review.
Subjects were followed up by the HF programs at their respective
institutions, which provided for the high likelihood that all major
events were captured. Heart transplantation, left ventricular assist
device (LVAD) implantation, and cardiac-related death were con-
sidered major events. Any death with a cardiac-related discharge
diagnosis was considered an event. The most common causes of
cardiac mortality, as per discharge diagnosis, were sudden cardiac
death (45%) and HF (55%). Clinicians conducting the CPX were not
involved in decisions regarding cause of death or heart transplant/
LVAD implantation. All subjects who did not experience a cardiac-
related event were followed up for the entire 24-month period.

Statistical Analysis
All continuous data are reported as mean ± SD. Receiver operating
classification (ROC) curve analysis was used to assess Ve/VCO2
slope and peak Vo2 classification schemes. A z test was used to
compare area under the ROC curve for the Ve/VCO2 slope and peak
Vo2. One-way ANOVA was used to assess differences in key
continuous variables, whereas y analysis assessed differences in key
categorical variables among the ventilatory classification groups.
Tukey’s honestly significant difference was used to determine
groups that were significantly different when the 1-way ANOVA
probability value was less than 0.05. Multivariate Cox regression
analysis assessed the combined prognostic power of the Ve/VCO2
slope, peak Vo2, age, LVEF, New York Heart Association (NYHA)
class, and cause of HF. Univariate Cox regression analysis was used
to assess the independent prognostic value of key baseline and CPX
variables and to assess hazard ratios for the ventilatory classification system developed by ROC curve analysis. Kaplan-Meier analysis
assessed survival characteristics of the Ve/VCO2 slope classification system and peak Vo2 developed by ROC curve analysis. The log-rank
test determined statistical significance on the Kaplan-Meier analysis.
ROC curve and Kaplan-Meier analyses also assessed the prognostic
ability of the Ve/VCO2 slope in the following subgroups: (1) only

TABLE 1. Studies Evaluating the Prognostic Validity of Ve/VCO2 Slope Versus
Peak Vo2

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients</th>
<th>Ve/VCO2 Slope Cutoff</th>
<th>Ve/VCO2 Slope Superiority Versus Peak Vo2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chua et al9</td>
<td>104</td>
<td>34</td>
<td>Yes</td>
</tr>
<tr>
<td>Francis et al9</td>
<td>203</td>
<td>Range, 30 to 55</td>
<td>Yes</td>
</tr>
<tr>
<td>Kleber et al6</td>
<td>144</td>
<td>&gt;130% of predicted</td>
<td>Yes</td>
</tr>
<tr>
<td>Pongkonski et al2</td>
<td>344</td>
<td>34</td>
<td>Yes</td>
</tr>
<tr>
<td>Corra et al6</td>
<td>600</td>
<td>35</td>
<td>Yes</td>
</tr>
<tr>
<td>Gitt et al10</td>
<td>233</td>
<td>34</td>
<td>Yes</td>
</tr>
<tr>
<td>Guazzi et al11</td>
<td>100</td>
<td>34</td>
<td>Yes</td>
</tr>
<tr>
<td>Arena et al4</td>
<td>213</td>
<td>34</td>
<td>Yes</td>
</tr>
<tr>
<td>Guazzi et al12</td>
<td>409</td>
<td>34</td>
<td>Yes in diastolic HF, similar in systolic HF</td>
</tr>
<tr>
<td>Nanas et al13</td>
<td>98</td>
<td>34</td>
<td>Yes</td>
</tr>
<tr>
<td>Tsurugaya et al14</td>
<td>215</td>
<td>34</td>
<td>Yes</td>
</tr>
</tbody>
</table>

TABLE 2. Univariate Cox Regression Results

<table>
<thead>
<tr>
<th>Variable</th>
<th>( \chi^2 )</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ve/VCO2 slope</td>
<td>72.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NYHA class</td>
<td>47.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak Vo2</td>
<td>29.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEF</td>
<td>24.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age</td>
<td>1.1</td>
<td>0.30</td>
</tr>
<tr>
<td>Cause of HF</td>
<td>0.65</td>
<td>0.42</td>
</tr>
</tbody>
</table>
subjects prescribed a β-blocker; (2) only subjects undergoing CPX on or after January 1, 2000; (3) only subjects with LVEF ≤40%; (4) only subjects undergoing CPX on a treadmill; and (5) only subjects undergoing CPX on a lower-extremity ergometer. Statistical differences with a probability value <0.05 were considered significant.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

There were 81 major cardiac events (64 deaths, 10 heart transplants, and 7 LVAD implantations) during the 2-year tracking period after CPX. The annual event rate was 9.5%. Univariate and multivariate Cox regression analyses results are listed in Tables 2 and 3, respectively. The Ve/VCO₂ slope, NYHA class, peak VO₂, and LVEF were all significant univariate predictors. The Ve/VCO₂ slope was the strongest predictor of major cardiac events in the multivariate analysis. NYHA class and LVEF added significant value and were retained in the regression. Peak VO₂, cause of HF, and age did not add significant predictive value and were removed from the multivariate regression.

ROC analysis revealed the prognostic classification schemes for Ve/VCO₂ slope (area under the curve 0.78, 95% CI 0.73 to 0.83, P<0.001) and peak VO₂ (area under the curve 0.71, 95% CI 0.65 to 0.77, P<0.001) were significant. The z test, however, found the Ve/VCO₂ slope classification scheme was significantly better than peak VO₂ (z score 2.34, P<0.01). The ROC curve for Ve/VCO₂ slope found a value of 29.9 produced a specificity of 95%, and a value of 45.0 produced a sensitivity of 95%. A Ve/VCO₂ slope value of 36.0 produced an optimal balance of sensitivity and specificity (74%/67%). From the Ve/VCO₂ slope ROC analysis, the following 4-level ventilatory classification system was developed: Ventilatory class (VC) I (VC-I) ≤29.9, VC-II 30.0 to 35.9; VC-III 36.0 to 44.9, and VC-IV ≥45.0. One-way ANOVA and χ² results are listed in Table 4. Peak VO₂ and NYHA class were significantly different among all 4 VC groups. A greater percentage of females were in VC-IV than in VC-I through VC-III. LVEF was higher in VC-I than in VC-II through VC-IV. Pharmacological intervention was comparable among groups with the exception of diuretics, for which the percentage of subjects increased from VC-I through VC-IV. β-Blocker use was also slightly higher in VC-IV.

Compared with subjects in VC-I, the hazard ratios for subjects in VC-II through VC-IV were 5.6 (95% CI 1.9 to 16.2, P=0.002), 11.4 (95% CI 4.0 to 32.5, P<0.001), and 28.0 (95% CI 9.7 to 80.8, P<0.001), respectively. Kaplan-Meier analysis results for the ventilatory classification system are illustrated in Figure 1. Survival characteristics were distinct among the 4 VC groups.

Peak VO₂ was also divided into 4 groups by ROC curve analysis. The ROC curve for peak VO₂ found a value of 8.9 mL of O₂·kg⁻¹·min⁻¹ produced a specificity of 95% and a value of 21.0 mL of O₂·kg⁻¹·min⁻¹ produced a sensitivity of 95%. A peak VO₂ value of 13.0 mL of O₂·kg⁻¹·min⁻¹ produced an optimal balance of sensitivity and specificity (73%/54%). Kaplan-Meier analysis revealed the percent of subjects who were event free in the ≤8.9, 9.0 to 13.0, 13.1 to 20.9, and ≥21.0 mL of O₂·kg⁻¹·min⁻¹ peak VO₂ subgroups was 94.6% (5/92), 84.8% (32/210), 74.1% (29/112), and 55.9% (15/28), respectively (log-rank 35.0, P<0.001). Although the 4-level prognostic classification system–based

TABLE 3. Multivariate Cox Regression Results

<table>
<thead>
<tr>
<th>Variable</th>
<th>χ²</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ve/VCO₂ slope</td>
<td>72.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NYHA class</td>
<td>17.8 (Residual χ²)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEF</td>
<td>6.8 (Residual χ²)</td>
<td>0.009</td>
</tr>
<tr>
<td>Cause of HF</td>
<td>1.2 (Residual χ²)</td>
<td>0.27</td>
</tr>
<tr>
<td>Peak VO₂</td>
<td>0.32 (Residual χ²)</td>
<td>0.57</td>
</tr>
<tr>
<td>Age</td>
<td>0.003 (Residual χ²)</td>
<td>0.96</td>
</tr>
</tbody>
</table>

Overall Group: n=448
VC-I (n=144): 56.9±13.0
VC-II (n=149): 56.6±13.4
VC-III (n=112): 56.5±12.9
VC-IV (n=43): 58.9±11.7

Sex, % male/female†‡: 78.8/21.2
LVEF, %*: 32.5±13.2
NYHA, mean (No. in IV/III/II/I): 2.0±0.67 (151/155/126/16)
Cause of HF, % nonischemic/sclerotic: 44.9/55.1
Peak VO₂, mL of O₂·kg⁻¹·min⁻¹*: 16.5±6.2
Ve/VCO₂ slope†: 33.9±8.6
Peak respiratory exchange ratio: 1.08±0.16
Prescribed ACE inhibitor, %: 71.5
Prescribed diuretic, %*: 55.6
Prescribed β-blocker, %‡: 53.8

ACE indicates angiotensin-converting enzyme.
†All VC groups significantly different, P<0.05.
‡VC-I significantly different from VC-II, VC-III, and VC-IV, P<0.05.
*VC-II significantly different from VC-I, VC-III, and VC-IV, P<0.05.
*VC-III significantly different from VC-I, VC-II, and VC-IV, P<0.05.
‡VC-I significantly different from VC-III, P<0.05.
*VC-IV significantly different from VC-I, VC-II, and VC-III, P<0.05.
peak Vo2 was also significant, the VC system was superior, as indicated by differences in log-rank score (86.8 versus 35.0).

Table 5 lists the percentage of subjects who had major cardiac events according to both the 4-level V˙E/V˙CO2 slope and peak V˙O was also significant, the VC system was superior, as indicated by differences in log-rank score (86.8 versus 35.0).

Results from the ROC and Kaplan-Meier analyses in the 5 subgroups are listed in Table 6. The prognostic characteristics of the V˙E/V˙CO2 slope were unaltered when only we considered subjects receiving a β-blocker, subjects tested on or after January 1, 2000, subjects with an LVEF ≤40%, subjects undergoing CPX on a treadmill only, and subjects undergoing CPX on a lower-extremity ergometer only.

### Previous Classification Based on CPX Testing

In 1982, Weber et al25 introduced a CPX-based classificatory system with the intent to better stratify HF hemodynamic severity using peak Vo2, which consistently reflects cardiac output changes during exercise. Four classes of Vo2 at peak exercise were proposed. Subsequently, the prognostic power of peak Vo2 was considered,2 and the identification of a severely reduced peak Vo2 (<10 mL of o2 · kg⁻¹ · min⁻¹) is still considered an absolute indication for listing patients for transplantation.26 More recently, however, a growing body of evidence has identified the V˙E/V˙CO2 slope as a superior prognostic marker compared with peak Vo2 (Table 1). Interestingly, this variable holds prognostic significance even when overall exercise performance is not severely compromised.7 A primary reason for this discrepancy may be the dependence of peak Vo2 on subject effort for optimal prognostic value, whereas the V˙E/V˙CO2 is primarily effort-independent.27 For example, consideration of a hypothetical male subject putting forth a submaximal effort and presenting with a peak Vo2 of 9.7 mL of o2 · kg⁻¹ · min⁻¹ leads to a misclassification of high risk for adverse events. This same hypothetical subject, however, also demonstrates a V˙E/V˙CO2 slope of 28.5, which more accurately classifies him as being at low risk. In addition, several investigations have shown that the V˙E/V˙CO2 slope retains its prognostic significance across a range of clinical conditions, including in the presence of submaximal effort,28 in patients with HF secondary to diastolic left ventricular dysfunction,12 and in HF patients prescribed a β-blocker.29 The fact that the prognostic characteristics of the V˙E/V˙CO2 slope were unaltered in the present

### TABLE 5. Percentage of Subjects Who Had a Major Cardiac Event Based on V˙E/V˙CO2 Slope and Peak V˙O2

<table>
<thead>
<tr>
<th>V˙E/V˙CO2 Slope Level</th>
<th>Peak V˙O2 Level, mL of o2 · kg⁻¹ · min⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤8.9</td>
</tr>
<tr>
<td>≤29.9</td>
<td>0 (0/4)</td>
</tr>
<tr>
<td>30.0–35.9</td>
<td>14.3 (1/7)</td>
</tr>
<tr>
<td>36.0–44.9</td>
<td>44.4 (4/9)</td>
</tr>
<tr>
<td>≥45.0</td>
<td>71.4 (10/14)</td>
</tr>
</tbody>
</table>

Values are percentages (no. of subjects experiencing major cardiac event/No. of subjects in group).
subgroup analyses further supports the robustness of this CPX variable.

**Insights on V˙E/V˙CO2 Slope Prognostic Value**

Several investigations have examined the correlation between V˙E/V˙CO2 slope and other markers of pathophysiology associated with HF, including abnormal pulmonary hemodynamics, exaggerated chemoreceptor and ergoreceptor sensitivity, and heart rate variability.30–32 In these studies, increasing V˙E/V˙CO2 slopes were related to progressively worsening hemodynamics, increased chemoreceptor and ergoreceptor activation, and decreased heart rate variability. Therefore, the increasingly worse prognosis as the V˙E/V˙CO2 slope increased in the present study likely reflects greater cardiovascular dysfunction compared with individuals with lower V˙E/V˙CO2 slope responses.

All previous studies examining the prognostic value of the V˙E/V˙CO2 slope have defined normal versus abnormal values in a dichotomous fashion.3,4,7 The most common threshold value for defining an abnormal V˙E/V˙CO2 slope has been in the order of ≥34. The present study revealed that the V˙E/V˙CO2 slope threshold value with an optimal balance of sensitivity and specificity was 36, which approximates the value used in previous studies to define normal versus abnormal. The present results, however, demonstrate that dichotomous expression of the V˙E/V˙CO2 slope may not be optimal. Rather, a 4-level classification system appears to better discriminate various levels of risk for adverse cardiac events in HF patients and optimizes the clinical utility of the variable. For example, if the V˙E/V˙CO2 slope was used as one of the clinical variables guiding listing for heart transplantation, a value between 36.0 and 44.9, although clearly abnormal, would not be afforded the same concern for adverse events as a value ≥45.0. Dichotomous expression of the V˙E/V˙CO2 slope with a threshold value of 36 would not allow for this distinction.

In a landmark paper, Francis et al8 divided a cohort of patients with HF according to V˙E/V˙CO2 slope quartiles and demonstrated a clear separation in survival among the 4 groups. Although this was done without consideration of sensitivity/specificity characteristics, the V˙E/V˙CO2 slope cut points used to define the 4 groups were strikingly similar to what is reported in the present investigation (27.7, 27.7 to 34.5, 34.6 to 42.1, and ≥42.1 versus 29.9, 30.0 to 35.9, 36.0 to 44.9, and ≥45.0). Furthermore, with the exception of age, variables retained in the multivariate Cox regression analysis were identical between the 2 studies, with the V˙E/V˙CO2 slope being the strongest prognostic marker. Another important similarity between the report by Francis et al8 and the present study is the comparison between the V˙E/V˙CO2 slope and peak Vo2. This analysis further reinforces the evidence that the V˙E/V˙CO2 slope is a superior marker. Overall, the combined findings of the present study and those reported by Francis et al strengthen the case for a multiple-level classification system based on the V˙E/V˙CO2 slope. Notably, a potential advantage of the present study is that most of the patients were tested during or after 2000, whereas in the study by Francis et al,8 all patients were tested during or before 1996, which implies that the cohort in the present investigation is more representative of present-day treatment of HF.

### TABLE 6. Prognostic Characteristics of V˙E/V˙CO2 Slope in Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>ROC Curve Analysis</th>
<th>Kaplan-Meier Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-Blockade (n=241)</td>
<td>Area, 0.80; 95% CI, 0.74–0.87; P&lt;0.001</td>
<td>VC-I 78 3 96.2 51.1, P&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VC-II 78 11 85.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VC-III 59 18 69.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VC-IV 26 15 42.3</td>
</tr>
<tr>
<td>CPX after 1/1/2000 (n=293)</td>
<td>Area, 0.76; 95% CI, 0.70–0.83; P&lt;0.001</td>
<td>VC-I 101 4 96.0 41.2, P&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VC-II 94 15 84.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VC-III 69 18 73.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VC-IV 29 14 51.7</td>
</tr>
<tr>
<td>LVEF ≤40% (n=340)</td>
<td>Area, 0.76; 95% CI, 0.70–0.82; P&lt;0.001</td>
<td>VC-I 96 4 95.8 62.6, P&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VC-II 110 20 81.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VC-III 97 29 70.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VC-IV 37 22 40.5</td>
</tr>
<tr>
<td>CPX on treadmill only (n=350)</td>
<td>Area, 0.79; 95% CI, 0.73–0.85; P&lt;0.001</td>
<td>VC-I 123 2 98.4 62.8, P&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VC-II 110 13 88.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VC-III 81 19 76.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VC-IV 36 17 52.8</td>
</tr>
<tr>
<td>CPX on extremity ergometer only (n=98)</td>
<td>Area, 0.77; 95% CI, 0.67–0.87; P&lt;0.001</td>
<td>VC-I 21 2 90.5 35.9, P&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VC-II 39 9 76.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VC-III 31 12 61.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VC-IV 7 7 0.0</td>
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</tbody>
</table>

**Arena et al V˙E/V˙CO2 Slope and Heart Failure 5**
VE/VCO₂ Slope Classification System Implications

Given the present findings, we propose a clinical algorithm for patients with HF using the VE/VCO₂ slope obtained during CPX, which is illustrated in Figure 2. This algorithm is hypothetical, and future investigations are required to confirm our findings.

For subjects in VC-I, the risk for adverse events appear to be negligible, and medical management would be appropriate. Both β-blockade and angiotensin-converting enzyme inhibition have been shown to significantly reduce the VE/VCO₂ slope in patients with HF. Medical management for patients who fall into VCs II through IV should be reviewed and optimized when indicated. Aerobic exercise training has been shown to significantly reduce the VE/VCO₂ slope and improve a host of other markers that suggest improved prognosis and should therefore be considered irrespective of VC. However, the effects of exercise training on morbidity and mortality in HF patients have been variable in smaller studies, and a large, multicenter exercise trial (HF-ACTION [Heart Failure: A Controlled Trial Investigating Outcomes of exercise trainNIng]) is currently under way. Cardiac resynchronization therapy has been shown to significantly reduce the VE/VCO₂ slope and improve a host of other markers that suggest improved prognosis and should therefore be considered irrespective of VC. However, the effects of exercise training on morbidity and mortality in HF patients have been variable in smaller studies, and a large, multicenter exercise trial (HF-ACTION [Heart Failure: A Controlled Trial Investigating Outcomes of exercise trainNIng]) is currently under way. Cardiac resynchronization therapy has been shown to significantly reduce the VE/VCO₂ slope and improve a host of other markers that suggest improved prognosis and should therefore be considered irrespective of VC.

Figure 2. Hypothetical ventilatory class clinical algorithm for optimal use of the VE/VCO₂ slope. CRT indicates cardiac resynchronization therapy.

The initial response to CPX. A shorter duration between CPX evaluations is important as VC class increases because the likelihood of an adverse event in the short term is greater, and it is important to quickly determine whether alternative medical management strategies should be considered. We recognize that the differences in survival characteristics in VC-II and VC-III may not be considered poor enough to warrant consideration of drastic interventions such as heart transplantation; however, this algorithm should also be viewed as a tool to guide minor adjustments in clinical management. For example, consider the patient with a VE/VCO₂ slope of 32.0 (VC-II) who is found to be taking a suboptimal dose of β-blockade. Increasing this medication may reduce the VE/VCO₂ slope and place the patient in VC-I, potentially reducing 2-year mortality risk by 10%.

Although the present study includes several hundred subjects with a substantial number of adverse events, the relatively low overall number of individuals in VC-IV must be considered a weakness of the study. Assessment of the proposed VC system in other HF cohorts is therefore encouraged to validate these findings. In addition, a host of other clinical variables, such as peak VO₂, LVEF, and neurohormonal markers, also possess predictive value, and CPX is just one of several important components of the prognostic paradigm in patients with HF. Although we were not able to perform a thorough assessment of all key prognostic markers presently available in the HF population, future research should consider the VC system in the context of a wider application of clinical and exercise test variables. Finally, subjects with diastolic dysfunction were included in the present investigation. Although we were able to perform a meaningful subgroup analysis in the subjects with systolic HF, we were unable to do so in the subjects with diastolic dysfunction (subjects with LVEF ≤50%; n=57, 5 events). We have previously demonstrated that the VE/VCO₂ slope
(expressed dichotomously) is prognostically significant and superior to peak \( \dot{V}O_2 \) in a small group of subjects with diastolic dysfunction.\textsuperscript{12} Future research should therefore also be directed toward validating the proposed ventilatory class system in a larger diastolic HF cohort.

**Perspectives and Conclusions**

Although peak \( \dot{V}O_2 \) has traditionally been used as the cornerstone of risk stratification in HF patients, recent investigations have pointed to ventilatory efficiency (VE/V\( \dot{CO}_2 \) slope) as a stronger prognostic factor across a wide scope of patients with HF. The present study demonstrates that a ventilatory class system based on VE/V\( \dot{CO}_2 \) quartiles can dramatically improve the predictive power of CPX beyond that obtained from peak \( \dot{V}O_2 \), NYHA classification, or the currently employed dichotomous VE/V\( \dot{CO}_2 \) slope model. On the basis of these findings, we advocate that this new ventilatory class system be incorporated into the current risk stratification guidelines.

**Disclosures**

None.

**References**

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**CLINICAL PERSPECTIVE**

Clinical trials have consistently demonstrated that cardiopulmonary exercise testing is a valuable tool in the clinical and prognostic assessment of patients with heart failure. The relationship between minute ventilation (Ve) and carbon dioxide production (VCO2), typically expressed as the slope of their incremental relationship during a symptom-limited exercise test, appears to be one of the strongest prognostic markers obtained from cardiopulmonary exercise testing. In fact, a number of previous investigations have shown that the Ve/VCO2 slope is prognostically superior to peak oxygen consumption (VO2). Despite the consistent findings of previous reports, peak VO2 remains the most frequently assessed cardiopulmonary exercise testing variable in clinical practice. The present study adds to the body of evidence demonstrating the prognostic superiority of the Ve/VCO2 slope over peak VO2 and furthermore proposes a 4-level ventilatory classification system (VC-I to VC-IV). This classification system, based on the Ve/VCO2 slope, may provide clinicians with important information regarding the potential risk for future adverse events and may help to guide therapeutic strategies. In conclusion, clinicians responsible for the interpretation of cardiopulmonary exercise testing data in patients with heart failure should consider the prognostic information the Ve/VCO2 slope appears to provide across heart failure populations with different levels of disease severity.