# 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 ($\dot{V}E$)–carbon dioxide production ($\dot{V}CO_2$) 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 $\dot{V}E/\dot{V}CO_2$ slope by developing a ventilatory class system that correlates $\dot{V}E/\dot{V}CO_2$ cut points to cardiac-related events.

***Methods and Results***—Four hundred forty-eight subjects diagnosed with heart failure were included in this analysis. The $\dot{V}E/\dot{V}CO_2$ 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 $\dot{V}E/\dot{V}CO_2$ 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 $\dot{V}E/\dot{V}CO_2$ 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:&NA;-.)**

**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 ($\dot{V}O$) was the first CPX variable to demonstrate prognostic value[2] 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 ($\dot{V}E/\dot{V}CO_2$) slope, is a strong prognostic marker in patients with HF.[3–7] The majority of studies report the $\dot{V}E/\dot{V}CO_2$ slope to be prognostically superior to peak $\dot{V}O$, which underscores the clinical importance of assessing ventilatory efficiency in HF patients (Table 1).

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Furthermore, a number of studies define a $\dot{V}E/\dot{V}CO_2$ slope of $\approx$34 as a threshold value for predicting a poorer prognosis (Table 1).[3,4,7] Although this dichotomous threshold has proven to be prognostically significant, the wide range of $\dot{V}E/\dot{V}CO_2$ 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 $\dot{V}E/\dot{V}CO_2$ 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;

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From the Department of Physical Therapy (R.A.) and Department of Internal Medicine (M.A.P.), Virginia Commonwealth University, Health Sciences Campus, Richmond, Va; VA Palo Alto Health Care System (J.M., J.A.), Cardiology Division, Stanford University, Palo Alto, Calif; LeBauer Cardiovascular Research Foundation (D.B., P.C.), Greensboro, NC; and University of Milano (M.G.), San Paolo Hospital, Cardiopulmonary Laboratory, Cardiology Division, University of Milano, San Paolo Hospital, Milano, Italy.

Correspondence to Ross Arena, PhD, PT, Assistant Professor, Department of Physical Therapy, Box 980224, Virginia Commonwealth University, Health Sciences Campus, Richmond, VA 23298-0224. E-mail raarena@.vcu.edu



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**TABLE 1. Studies Evaluating the Prognostic Validity of $\dot{V}e/\dot{V}co_2$ Slope Versus Peak $\dot{V}o_2$**

| Reference | Patients | $\dot{V}e/\dot{V}co_2$ Slope Cutoff | $\dot{V}e/\dot{V}co_2$ Slope Superiority Versus Peak $\dot{V}o_2$ |
|---|---|---|---|
| Chua et al[3] | 104 | 34 | Yes |
| Francis et al[8] | 203 | Range, 30 to 55 | Yes |
| Kleber et al[6] | 144 | >130% of predicted | Yes |
| Ponikowski et al[7] | 344 | 34 | Yes |
| Corra et al[9] | 600 | 35 | Yes |
| Gitt et al[10] | 233 | 34 | Yes |
| Guazzi et al[11] | 100 | 34 | Yes |
| Arena et al[4] | 213 | 34 | Yes |
| Guazzi et al[12] | 409 | 34 | Yes in diastolic HF, similar in systolic HF |
| Nanas et al[13] | 98 | 34 | Yes |
| Tsurugaya et al[14] | 215 | 34 | Yes |

Virginia Commonwealth University, Richmond, Va; LeBauer Cardiovascular Research Foundation, Greensboro, NC; and the VA Palo Alto Health Care System and Stanford University, Palo Alto, Calif. A total of 448 consecutive patients with chronic HF who were tested between March 18, 1993, and February 8, 2006, were included. Inclusion criteria consisted of a diagnosis of HF[15] and evidence of left ventricular systolic and/or diastolic dysfunction by 2D echocardiography obtained within 1 month of exercise testing. Subjects were classified as having systolic HF if they presented with a left ventricular ejection fraction (LVEF) ≤45%. Subjects with an LVEF ≥50% and indications of an abnormal filling pattern were classified as having diastolic dysfunction.[16] The percentage of subjects with an implanted cardiac resynchronization device and/or internal cardioverter defibrillator was ≈9%. Subjects received routine follow-up care at the 5 institutions included in the present 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 with treadmill[17] or cycle ergometry[18] 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 their metabolic exercise testing equipment by exercising a healthy subject at a submaximal steady rate to verify measured $\dot{V}O$ matched estimated $\dot{V}O$ from the workload.[19] Previous studies have demonstrated optimal peak $\dot{V}O$ and $\dot{V}E/\dot{V}CO_2$ slope prognostic threshold values are similar regardless of the mode of exercise in patients with HF.[20] 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 ($\dot{V}E$), oxygen uptake ($\dot{V}O$), carbon dioxide output ($\dot{V}CO_2$), and other cardiopulmonary variables were acquired on a breath-by-breath basis and averaged over 10- or 15-second intervals. Peak $\dot{V}O$ and peak respiratory exchange ratio were expressed as the highest averaged samples obtained during the exercise test. $\dot{V}E$ and $\dot{V}CO_2$ values, acquired from the initiation of exercise to peak exercise, were input into spreadsheet software (Microsoft Excel, Microsoft Corp, Redmond, Wash) to calculate the $\dot{V}E/\dot{V}CO_2$ 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 $\dot{V}E/\dot{V}CO_2$ slope is prognostically optimal.[21,22]

## 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 considered 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 characteristic (ROC) curve analysis was used to assess $\dot{V}E/\dot{V}CO_2$ slope and peak $\dot{V}O$ classification schemes. A $z$ test was used to compare area under the ROC curve for the $\dot{V}E/\dot{V}CO_2$ slope and peak $\dot{V}O$.[23] One-way ANOVA was used to assess differences in key continuous variables, whereas $\chi^2$ 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 $\dot{V}E/\dot{V}CO_2$ slope, peak $\dot{V}O$, 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 $\dot{V}E/\dot{V}CO_2$ slope classification system and peak $\dot{V}O$ 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 $\dot{V}E/\dot{V}CO_2$ slope in the following subgroups: (1) only

**TABLE 2. Univariate Cox Regression Results**

| Variable | $\chi^2$ | $P$ |
|---|---|---|
| $\dot{V}e/\dot{V}co_2$ slope | 72.6 | <0.001 |
| NYHA class | 47.9 | <0.001 |
| Peak $\dot{V}o_2$ | 29.4 | <0.001 |
| LVEF | 24.9 | <0.001 |
| Age | 1.1 | 0.30 |
| Cause of HF | 0.65 | 0.42 |

**TABLE 3. Multivariate Cox Regression Results**

| Variable | $\chi^2$ | $P$ |
|---|---|---|
| $\dot{V}e/\dot{V}co_2$ slope | 72.6 | <0.001 |
| NYHA class | 17.8 (Residual $\chi^2$) | <0.001 |
| LVEF | 6.8 (Residual $\chi^2$) | 0.009 |
| Cause of HF | 1.2 (Residual $\chi^2$) | 0.27 |
| Peak $\dot{V}o_2$ | 0.32 (Residual $\chi^2$) | 0.57 |
| Age | 0.003 (Residual $\chi^2$) | 0.96 |

subjects prescribed a $\beta$-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 $\dot{V}E/\dot{V}CO_2$ slope, NYHA class, peak $\dot{V}O$, and LVEF were all significant univariate predictors. The $\dot{V}E/\dot{V}CO_2$ 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 $\dot{V}O$, 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 $\dot{V}E/\dot{V}CO_2$ slope (area under the curve 0.78, 95% CI 0.73 to 0.83, $P<0.001$) and peak $\dot{V}O$ (area under the curve 0.71, 95% CI 0.65 to 0.77, $P<0.001$) were significant. The $z$ test, however, found the $\dot{V}E/\dot{V}CO_2$ slope classification scheme was significantly better than peak $\dot{V}O$ ($z$ score 2.34, $P<0.01$). The ROC curve for $\dot{V}E/\dot{V}CO_2$ slope found a value of 29.9 produced a specificity of 95%, and a value of 45.0 produced a sensitivity of 95%. A $\dot{V}E/\dot{V}CO_2$ slope value of 36.0 produced an optimal balance of sensitivity and specificity (74%/67%). From the $\dot{V}E/\dot{V}CO_2$ 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 $\chi^2$ results are listed in Table 4. Peak $\dot{V}O$ 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. $\beta$-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 $\dot{V}O$ was also divided into 4 groups by ROC curve analysis. The ROC curve for peak $\dot{V}O$ found a value of 8.9 mL of $O_2 \cdot kg^{-1} \cdot min^{-1}$ produced a specificity of 95% and a value of 21.0 mL of $O_2 \cdot kg^{-1} \cdot min^{-1}$ produced a sensitivity of 95%. A peak $\dot{V}O$ value of 13.0 mL of $O_2 \cdot kg^{-1} \cdot min^{-1}$ 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 $O_2 \cdot kg^{-1} \cdot min^{-1}$ peak $\dot{V}O$ subgroups was 94.6% (5/92), 84.8% (32/210), 74.1% (29/112), and 55.9% (15/34), respectively (log-rank 35.0, $P<0.001$). Although the 4-level prognostic classification system–based

**TABLE 4. Baseline Characteristics of the Population**

| | Overall Group (n=448) | VC-I (n=144) | VC-II (n=149) | VC-III (n=112) | VC-IV (n=43) |
|---|---|---|---|---|---|
| Age, y | 56.9±13.0 | 56.6±13.4 | 56.5±12.9 | 58.9±11.7 | 53.8±14.7 |
| Sex, % male/female*‡ | 78.8/21.2 | 89.6/10.4 | 73.8/26.2 | 78.6/21.4 | 60.5/39.5 |
| LVEF, %*‖ | 32.5±13.2 | 37.0±13.1 | 32.9±12.4 | 28.2±12.2 | 27.8±13.7 |
| NYHA, mean (No. in I/II/III/IV)† | 2.0±0.87 (151/155/126/16) | 1.5±0.74 (91/33/18/2) | 2.0±0.78 (42/69/35/3) | 2.4±0.77 (16/41/51/4) | 2.8±0.77 (2/12/22/7) |
| Cause of HF, % nonischemic/ischemic‖ | 44.9/55.1 | 43.7/56.3 | 49.7/50.3 | 37.7/63.3 | 48.8/51.2 |
| Peak $\dot{V}o_2$, mL of $O_2 \cdot kg^{-1} \cdot min^{-1}$† | 16.5±6.2 | 20.4±6.9 | 16.3±5.1 | 13.8±4.0 | 10.9±3.5 |
| $\dot{V}e/\dot{V}co_2$ slope† | 33.9±8.6 | 25.6±3.2 | 32.6±1.7 | 39.5±2.5 | 52.1±7.7 |
| Peak respiratory exchange ratio | 1.08±0.16 | 1.10±0.19 | 1.07±0.14 | 1.07±0.15 | 1.10±0.15 |
| Prescribed ACE inhibitor, % | 71.5 | 71.5 | 70.9 | 71.7 | 67.4 |
| Prescribed diuretic, %*¶ | 55.6 | 39.6 | 54.7 | 69.0 | 76.7 |
| Prescribed $\beta$-blocker, %§ | 53.8 | 54.2 | 52.3 | 52.7 | 60.4 |

ACE indicates angiotensin-converting enzyme.
*VC-I significantly different from VC-II, VC-III, and VC-IV, $P<0.05$.
†All VC groups significantly different, $P<0.05$.
‡VC-IV significantly different from VC-I, VC-II, and VC-III, $P<0.05$.
§VC-II significantly different from VC-IV, $P<0.05$.
‖VC-II significantly different from VC-III, $P<0.05$.
¶VC-II significantly different from VC-III and VC-IV, $P<0.05$.

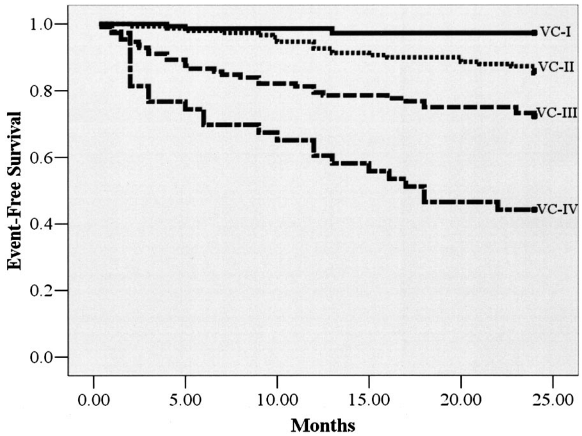


**Figure 1.** Kaplan-Meier analysis for 2-year major cardiac-related events. Subjects meeting criteria for VC-1 ($\dot{V}E/\dot{V}CO_2$ slope ≤29.9; n=144) experienced 4 major cardiac events (including 2 heart transplants); 97.2% were event-free. Subjects meeting VC-II criteria ($\dot{V}E/\dot{V}CO_2$ slope 30.0 to 35.9; n=149) experienced 22 major cardiac events (including 3 LVAD implantations); 85.2% were event-free. Subjects meeting VC-III criteria ($\dot{V}E/\dot{V}CO_2$ slope 36.0 to 44.9; n=112) experienced 31 major cardiac events (including 3 LVAD implantations and 2 heart transplants); 72.3% were event-free. Subjects who met VC-IV criteria ($\dot{V}E/\dot{V}CO_2$ slope ≥45.0; n=43) experienced 24 major cardiac events (including 2 LAVD implantations and 5 heart transplants); 44.2% were event-free. Log-rank 86.8, *P*<0.0001.

peak $\dot{V}O$ 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 $\dot{V}E/\dot{V}CO_2$ slope and peak $\dot{V}O$ classifications. Subjects with a $\dot{V}E/\dot{V}CO_2$ slope ≤29.9 demonstrated a favorable prognosis irrespective of peak $\dot{V}O$. Furthermore, the trends for increasing event rates were more apparent as the $\dot{V}E/\dot{V}CO_2$ slope increased (down columns) compared with decreasing peak $\dot{V}O$ (across rows). Although the number of subjects per subgroup was relatively small, the highest major cardiac event rate was observed in subjects with a $\dot{V}E/\dot{V}CO_2$ slope ≥45.0 and peak $\dot{V}O$ ≤8.9 mL of $O_2 \cdot kg^{-1} \cdot min^{-1}$.

Results from the ROC and Kaplan-Meier analyses in the 5 subgroups are listed in Table 6. The prognostic characteristics of the $\dot{V}E/\dot{V}CO_2$ slope were unaltered when only we considered subjects receiving a $\beta$-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.

## Discussion

In recent years, the $\dot{V}E/\dot{V}CO_2$ slope has gained considerable notoriety in the HF population as a valuable prognostic marker. This CPX variable is readily derived by software packages that operate present-day ventilatory expired gas units, which makes its clinical application as feasible as peak $\dot{V}O$. The present investigation demonstrates that a ventilatory class system based on selected $\dot{V}E/\dot{V}CO_2$ slope cut points dramatically refines the prognostic power of this variable across a wide spectrum of HF severity and further establishes the superiority of the $\dot{V}E/\dot{V}CO_2$ slope over peak $\dot{V}O$ and NYHA class for assessing prognosis in patients with HF. This information is new in itself and reinforces the body of evidence demonstrating a strong prognostic role for the $\dot{V}E/\dot{V}CO_2$ slope.[3–5,8,24]

### Previous Classification Based on CPX Testing

In 1982, Weber et al[25] introduced a CPX-based classificatory system with the intent to better stratify HF hemodynamic severity using peak $\dot{V}O$, which consistently reflects cardiac output changes during exercise. Four classes of $\dot{V}O$ at peak exercise were proposed. Subsequently, the prognostic power of peak $\dot{V}O$ was considered,[2] and the identification of a severely reduced peak $\dot{V}O$ (<10 mL of $O_2 \cdot kg^{-1} \cdot min^{-1}$) is still considered an absolute indication for listing patients for transplantation.[26] More recently, however, a growing body of evidence has identified the $\dot{V}E/\dot{V}CO_2$ slope as a superior prognostic marker compared with peak $\dot{V}O$ (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 $\dot{V}O$ on subject effort for optimal prognostic value, whereas the $\dot{V}E/\dot{V}CO_2$ is primarily effort-independent.[27] For example, consideration of a hypothetical male subject putting forth a submaximal effort and presenting with a peak $\dot{V}O$ of 9.7 mL of $O_2 \cdot kg^{-1} \cdot min^{-1}$ leads to a misclassification of high risk for adverse events. This same hypothetical subject, however, also demonstrates a $\dot{V}E/\dot{V}CO_2$ slope of 28.5, which more accurately classifies him as being at low risk. In addition, several investigations have shown that the $\dot{V}E/\dot{V}CO_2$ 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 $\beta$-blocker.[29] The fact that the prognostic characteristics of the $\dot{V}E/\dot{V}CO_2$ slope were unaltered in the present

**TABLE 5. Percentage of Subjects Who Had a Major Cardiac Event Based on $\dot{V}e/\dot{V}co_2$ Slope and Peak $\dot{V}o_2$**

| | Peak $\dot{V}o_2$ Level, mL of $o_2 \cdot kg^{-1} \cdot min^{-1}$ | | | |
|---|---|---|---|---|
| $\dot{V}e/\dot{V}co_2$ Slope Level | ≤8.9 | 9.0–13.0 | 13.1–20.9 | ≥21.0 |
| ≤29.9 | 0 (0/4) | 6.7 (1/15) | 4.5 (3/68) | 0 (0/57) |
| 30.0–35.9 | 14.3 (1/7) | 17.1 (6/35) | 15.6 (12/77) | 10.0 (3/30) |
| 36.0–44.9 | 44.4 (4/9) | 29.5 (13/44) | 22.2 (12/54) | 40.0 (2/5) |
| ≥45.0 | 71.4 (10/14) | 50.0 (9/18) | 45.5 (5/11) | No subjects in category |

Values are percentages (no. of subjects experiencing major cardiac event/No. of subjects in group).

**TABLE 6. Prognostic Characteristics of $\dot{V}e/\dot{V}co_2$ Slope in Subgroups**

| | | Kaplan-Meier Analysis | | | | |
|---|---|---|---|---|---|---|
| Subgroup | ROC Curve Analysis | VC Class | n | No. of Events | % Survival | Log-rank |
| β-Blockade (n=241) | Area, 0.80; 95% CI, 0.74–0.87; $P<0.001$ | VC-I | 78 | 3 | 96.2 | 51.1, $P<0.001$ |
| | | VC-II | 78 | 11 | 85.9 | |
| | | VC-III | 59 | 18 | 69.5 | |
| | | VC-IV | 26 | 15 | 42.3 | |
| CPX after 1/1/2000 (n=293) | Area, 0.76; 95% CI, 0.70–0.83; $P<0.001$ | VC-I | 101 | 4 | 96.0 | 41.2, $P<0.001$ |
| | | VC-II | 94 | 15 | 84.0 | |
| | | VC-III | 69 | 18 | 73.9 | |
| | | VC-IV | 29 | 14 | 51.7 | |
| LVEF ≤40% (n=340) | Area, 0.76; 95% CI, 0.70–0.82; $P<0.001$ | VC-I | 96 | 4 | 95.8 | 62.6, $P<0.001$ |
| | | VC-II | 110 | 20 | 81.8 | |
| | | VC-III | 97 | 29 | 70.1 | |
| | | VC-IV | 37 | 22 | 40.5 | |
| CPX on treadmill only (n=350) | Area, 0.79; 95% CI, 0.73–0.85; $P<0.001$ | VC-I | 123 | 2 | 98.4 | 62.8, $P<0.001$ |
| | | VC-II | 110 | 13 | 88.2 | |
| | | VC-III | 81 | 19 | 76.5 | |
| | | VC-IV | 36 | 17 | 52.8 | |
| CPX on extremity ergometer only (n=98) | Area, 0.77; 95% CI, 0.67–0.87; $P<0.001$ | VC-I | 21 | 2 | 90.5 | 35.9, $P<0.001$ |
| | | VC-II | 39 | 9 | 76.9 | |
| | | VC-III | 31 | 12 | 61.3 | |
| | | VC-IV | 7 | 7 | 0.0 | |

subgroup analyses further supports the robustness of this CPX variable.

## Insights on $\dot{V}E/\dot{V}CO_2$ Slope Prognostic Value

Several investigations have examined the correlation between $\dot{V}E/\dot{V}CO_2$ 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 $\dot{V}E/\dot{V}CO_2$ slopes were related to progressively worsening hemodynamics, increased chemoreceptor and ergoreceptor activation, and decreased heart rate variability. Therefore, the increasingly worse prognosis as the $\dot{V}E/\dot{V}CO_2$ slope increased in the present study likely reflects greater cardiovascular dysfunction compared with individuals with lower $\dot{V}E/\dot{V}CO_2$ slope responses.

All previous studies examining the prognostic value of the $\dot{V}E/\dot{V}CO_2$ slope have defined normal versus abnormal values in a dichotomous fashion.[3,4,7] The most common threshold value for defining an abnormal $\dot{V}E/\dot{V}CO_2$ slope has been in the order of ≥34. The present study revealed that the $\dot{V}E/\dot{V}CO_2$ 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 $\dot{V}E/\dot{V}CO_2$ 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 $\dot{V}E/\dot{V}CO_2$ 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 $\dot{V}E/\dot{V}CO_2$ slope with a threshold value of 36 would not allow for this distinction.

In a landmark paper, Francis et al[8] divided a cohort of patients with HF according to $\dot{V}E/\dot{V}CO_2$ slope quartiles and demonstrated a clear separation in survival among the 4 groups. Although this was done without consideration of sensitivity/specificity characteristics, the $\dot{V}E/\dot{V}CO_2$ 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 $\dot{V}E/\dot{V}CO_2$ slope being the strongest prognostic marker. Another important similarity between the report by Francis et al[8] and the present study is the comparison between the $\dot{V}E/\dot{V}CO_2$ slope and peak $\dot{V}O$. This analysis further reinforces the evidence that the $\dot{V}E/\dot{V}CO_2$ slope is a superior marker. Overall, the combined findings of the present study and those reported by Francis et al[8] strengthen the case for a multiple-level classification system based on the $\dot{V}E/\dot{V}CO_2$ 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.

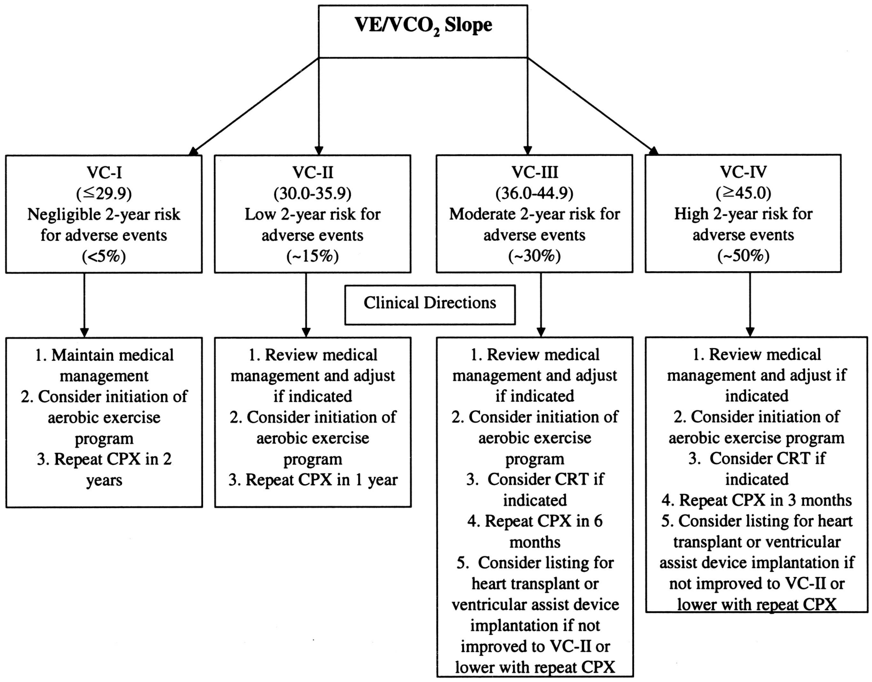


**Figure 2.** Hypothetical ventilatory class clinical algorithm for optimal use of the $\dot{V}E/\dot{V}CO_2$ slope. CRT indicates cardiac resynchronization therapy.

## $\dot{V}E/\dot{V}CO_2$ Slope Classification System Implications

Given the present findings, we propose a clinical algorithm for patients with HF using the $\dot{V}E/\dot{V}CO_2$ 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[33] and angiotensin-converting enzyme inhibition[34] have been shown to significantly reduce the $\dot{V}E/\dot{V}CO_2$ 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 $\dot{V}E/\dot{V}CO_2$ slope[35] and improve a host of other markers that suggest improved prognosis[36] 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 traiNing]) is currently under way. Cardiac resynchronization therapy has been shown to significantly reduce the $\dot{V}E/\dot{V}CO_2$ slope and should be considered for subjects in VC-III and VC-IV. Heart transplant or LVAD implantation should be considered for subjects in VC-III and VC-IV who do not improve to a lower class after optimization of pharmacological interventions, implementation of an aerobic training program, and consideration of cardiac resynchronization therapy. A key distinction among the 4 ventilatory classes is the timing of repeat exercise testing. We have previously demonstrated that the prognostic strength of CPX variables is reduced as time since testing increases.[37] Specifically, the number of events increases in subjects who initially demonstrate favorable $\dot{V}E/\dot{V}CO_2$ slope values. Reassessment is therefore necessary after a period of time regardless of 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 $\dot{V}E/\dot{V}CO_2$ slope of 32.0 (VC-II) who is found to be taking a suboptimal dose of β-blockade. Increasing this medication may reduce the $\dot{V}E/\dot{V}CO_2$ 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 $\dot{V}O$, LVEF,[8] and neurohormonal markers,[38] 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 $\dot{V}E/\dot{V}CO_2$ slope (expressed dichotomously) is prognostically significant and superior to peak $\dot{V}O$ in a small group of subjects with diastolic dysfunction.[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 $\dot{V}O$ has traditionally been used as the cornerstone of risk stratification in HF patients, recent investigations have pointed to ventilatory efficiency ($\dot{V}E/\dot{V}CO_2$ 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 $\dot{V}E/\dot{V}CO_2$ quartiles can dramatically improve the predictive power of CPX beyond that obtained from peak $\dot{V}O$, NYHA classification, or the currently employed dichotomous $\dot{V}E/\dot{V}CO_2$ 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.

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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 ($\dot{V}E$) and carbon dioxide production ($\dot{V}CO_2$), 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 $\dot{V}E/\dot{V}CO_2$ slope is prognostically superior to peak oxygen consumption ($\dot{V}O$). Despite the consistent findings of previous reports, peak $\dot{V}O$ 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 $\dot{V}E/\dot{V}CO_2$ slope over peak $\dot{V}O$ and furthermore proposes a 4-level ventilatory classification system (VC-I to VC-IV). This classification system, based on the $\dot{V}E/\dot{V}CO_2$ 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 $\dot{V}E/\dot{V}CO_2$ slope appears to provide across heart failure populations with different levels of disease severity.