Usefulness of ventilatory inefficiency in predicting prognosis across the heart failure spectrum

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Abstract

Aims The minute ventilation–carbon dioxide production relationship (VE/VCO2 slope) is widely used for prognostication in heart failure (HF) with reduced left ventricular ejection fraction (LVEF). This study explored the prognostic value of VE/VCO2 slope across the spectrum of HF defined by ranges of LVEF.

Methods and results In this single-centre retrospective observational study of 1347 patients with HF referred for cardiopulmonary exercise testing, patients with HF were categorized into HF with reduced (HFrEF, LVEF < 40%, n = 598), mid-range (HFmrEF, 40% ≤ LVEF < 50%, n = 164), and preserved (HFpEF, LVEF ≥ 50%, n = 585) LVEF. Four ventilatory efficiency categories (VC) were defined: VC-I, VE/VCO2 slope ≤ 29; VC-II, 29 < VE/VCO2 slope < 36; VC-III, 36 ≤ VE/VCO2 slope < 45; and VC-IV, VE/VCO2 slope ≥ 45. The associations of these VE/VCO2 slope categories with a composite outcome of all-cause mortality or HF hospitalization were evaluated for each category of LVEF. Over a median follow-up of 2.0 (interquartile range: 1.9, 2.0) years, 201 patients experienced the composite outcome. Compared with patients in VC-I, those in VC-II, III, and IV demonstrated three-fold, five-fold, and eight-fold increased risk for the composite outcome. This incremental risk was observed across HFrEF, HFmrEF, and HFpEF cohorts.

Conclusions Higher VE/VCO2 slope is associated with incremental risk of 2 year all-cause mortality and HF hospitalization across the spectrum of HF defined by LVEF. A multilevel categorical approach to the interpretation of VE/VCO2 slope may offer more refined risk stratification than the current binary approach employed in clinical practice.

Keywords Cardiopulmonary exercise test; VE/VCO2 slope; Ventilatory efficiency; Heart failure; Heart failure hospitalization

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Introduction

Cardiopulmonary exercise testing (CPET) measures cardiopulmonary reserve and provides an important prognostic tool in the management of heart failure (HF). In addition to peak oxygen consumption (peak VO2), the ratio of minute ventilation to carbon dioxide production (VE/VCO2 slope), a measure of ventilatory efficiency, strongly predicts adverse events in HF.1 In clinical practice, a single VE/VCO2 slope threshold defining abnormal, most commonly ≥36, is employed across the spectrum of HF categorized by left ventricular ejection fraction (LVEF).1–3 However, the predictive value of this VE/VCO2 slope threshold has largely been validated in patients with HF with reduced LVEF (HFrEF),4–7 and its application in patients with HF with mid-range LVEF (HFmrEF) and HF with preserved LVEF (HFpEF) requires additional validation.8–10

Moreover, a wide range of VE/VCO2 slope values are seen in clinical practice, and so risk stratification based on a single cut-point might underutilize the prognostic utility of VE/VCO2 slope. A multilevel categorization system developed in a small cohort (n = 448) of patients with HF, predominantly HFrEF (76%), correlated higher categories of VE/VCO2 slope cut-
points with increasing risk of cardiac-related events. Whether a similar classification could refine prognostication and clinical decision-making warrants further evaluation in a larger cohort of patients with HF, especially those with HFrEF or HFpEF. The objectives of this study were to evaluate and compare the prognostic utility of a multilevel VE/VCO₂ slope classification system across categories of HF defined by LVEF.

Methods

Study design

This was a single-centre, retrospective cohort study. Consecutive patients with a diagnosis of HF with known LVEF, who were clinically referred for CPET between June 2010 through December 2016 at Brigham and Women’s Hospital, were considered for inclusion in this study. Patients were diagnosed as having HF if they had (i) a diagnosis of HF in the electronic medical record (EMR), (ii) documented use of loop diuretics/metolazone, or (iii) cardiomyopathy defined as LVEF < 40%. HF was then categorized into HFrEF (LVEF < 40%), HFmrEF (40% ≤ LVEF < 50%), and HFpEF (LVEF ≥ 50%) based on LVEF derived either by transthoracic echocardiography (n = 1309) or cardiac magnetic resonance imaging (n = 38) performed within a median of 1 day [interquartile range (IQR) 0, 76 days] of CPET.

Patients were excluded if they had incomplete CPET data, any history of a left-ventricular-assist device (LVAD) or cardiac transplantation prior to date of CPET, or where CPET did not follow a ramp protocol on an upright cycle ergometer. The final cohort consisted of 1347 patients (Supporting Information, Figure S1). This study was approved by the Partners Healthcare System Institutional Review Board.

Clinical information

Demographics, indications for exercise testing, and cardiovascular (CV) history and medications were prospectively recorded at the time of CPET by the exercise physiologist using a structured patient interview and EMR review. Ischemic heart disease was defined as a history of myocardial infarction, coronary revascularization, or documented obstructive angiographic coronary artery disease. Hyperlipidemia was defined as a known diagnosis of hyperlipidemia or statin use at time of CPET. Diabetes mellitus was defined as a known diagnosis of diabetes mellitus or use of insulin or oral hypoglycaemic agents at time of CPET.

Cardiopulmonary exercise testing protocol

All CPETs were performed using a ramp protocol on an upright cycle ergometer (Lode Corival, Groningen, The Netherlands) with subjects breathing room air. Ventilatory expired gas analysis was performed using a metabolic cart (Breeze Suite 8.6.0.65 SP1, MGC Diagnostics, St. Paul, MN). Standard 12-lead electrocardiogram and blood pressures were obtained at rest, every 2 to 3 min during exercise, and for a period ≥4 min during the recovery phase. Baseline metabolic evaluation was performed during a 2- min rest period before exercise and during cool-down period for ≥1 min. VE, VO₂, and VCO₂ were acquired breath-by-breath and averaged for 10 s. Peak VO₂ was defined as the highest 10 s averaged VO₂ around the time of maximal effort. A set of previously published normative equations were used to estimate predicted peak VO₂. VE/VCO₂ slope was calculated by linear regression from the start of freewheel to the end of the test (peak exercise). All gas exchange calculations were performed automatically by the metabolic cart software and were manually verified by the exercise physiologist performing the test and subsequently by a cardiologist. Four ventilatory categories (VC) were defined based on previous work by Arena et al.: VC-I, VE/VCO₂ slope ≤ 29; VC-II, 29 < VE/VCO₂ slope ≤ 36; VC-III, 36 ≤ VE/VCO₂ slope ≤ 45; and VC-IV, VE/VCO₂ slope ≥ 45.

Study endpoints

The primary endpoint was a composite of all-cause mortality or HF hospitalization (whichever occurred first) occurring within 2 years of CPET. Events were included through 1 July 2017. Mortality was determined using the Partners Health Care Research Patient Data Registry (linked to the Social Security Death Index, updated 30 July 2017). HF hospitalizations were abstracted by EMR review and were defined as unplanned admissions with clinical presentations consistent with HF exacerbations requiring escalation of existing HF treatment or initiation of new therapies (Table S1). Patients who received a LVAD or cardiac transplant after the CPET date were right-censored at the time of this event. Patients who were lost to follow-up were also right-censored.

Statistical analyses

Continuous variables with approximately normal distributions are reported as means ± standard deviation and compared using one-way ANOVA across all three HF cohorts. Continuous, non-normal data are presented as medians with IQR and compared using the Kruskal–Wallis test. Categorical variables are presented as counts with percentages and compared using Fisher’s exact test. Median follow-up was estimated using the reverse Kaplan–Meier method. To examine the association between VE/VCO₂ slope category and the composite outcome, cause-specific Cox proportional-hazards regression models were used. The VE/VCO₂ slope category ≤ 29 (VC-I)
was used as the reference group. A cause-specific approach was used for modelling, as LVAD and cardiac transplant \((n = 34)\) were treated as competing risks; therefore, both events were right-censored. Unadjusted and adjusted (continuous age and gender) hazard ratios with 95% confidence intervals (CIs) were presented. Additionally, continuously measured VE/VCO\(_2\) slope was specified using restricted cubic splines with four knots in a model adjusting for age and gender. The number of knots was chosen using Akaike’s information criterion. All models were assessed for overly influential patients, proportional hazards, and linearity. Cumulative incidence curves of the composite outcome were compared across VE/VCO\(_2\) slope categories for each LVEF cohort using Gray’s test of equivalence.

Time-dependent receiver operating characteristic analysis was performed using the nearest neighbours approach to examine the performance of previously defined VE/VCO\(_2\) slope cut-offs (29 and 36)\(^3\) as predictors of the composite outcome at 2 year follow-up.\(^3,\)\(^11\) Sensitivity and specificity were calculated along with 95% CIs generated through bootstrapping using the percentile method.\(^4\) We independently determined VE/VCO\(_2\) slope cut-offs using Youden’s index (maximizing sensitivity + specificity) and bootstrapped CIs to allow for comparison across LVEF.

Receiver operating characteristic analysis was also used to compare the performance of peak VO\(_2\), VE/VCO\(_2\) slope, and the combination of peak VO\(_2\) and VE/VCO\(_2\) slope as predictors of the 2 year composite outcome. All hypothesis testing was two-tailed, and \(P\) values less than 0.05 were considered statistically significant. Statistical analyses were performed using SAS Version 9.4 (SAS Institute, Cary, North Carolina, USA).

### Results

#### Baseline demographics

The entire cohort of 1347 patients had a mean age of 58.0 \(\pm\) 14.6 years and was predominantly Caucasian (85.0%) and male (60.5%) (Table 1). Compared with HFmrEF and HFpEF cohorts, patients in the HFrEF cohort were more likely to be male, with a higher prevalence of diabetes, hypertension, hypercholesterolemia, ischaemic heart disease, and smoking (Table 1). All CV medications were more commonly prescribed in HFrEF compared with other cohorts (Table 1).

#### Cardiopulmonary exercise testing results

The mean peak VO\(_2\) for the entire cohort was 15.0 \(\pm\) 6.6 mL/kg/min with a mean peak respiratory exchange ratio of 1.16 \(\pm\) 0.14; more than half the cohort had peak VO\(_2\) < 14 mL/kg/min (Table 2). The median VE/VCO\(_2\) slope for the entire cohort was 32.0 (IQR 27.9, 38.4). Compared with patients with HFmrEF or HFpEF, pa-

| Table 1 Baseline demographics of the study cohorts |
|-----------------------------------------------|
| **Gender, male** | Entire cohort \((n = 1347)\) | HFrEF \((n = 598)\) | HFmrEF \((n = 164)\) | HFpEF \((n = 585)\) | \(P\) value |
|------------------|-----------------|-----------------|-----------------|-----------------|----------------|
| Age, years       | 58.0 ± 14.6     | 58.3 ± 13.1     | 55.8 ± 14.6     | 58.1 ± 16.0     | 0.12           |
| Body mass index (kg/m\(^2\)) | 29.0 ± 6.3     | 28.2 ± 5.4     | 28.8 ± 6.2     | 29.9 ± 7.1     | 0.0001         |
| Race\(^a\)       |                 |                 |                 |                 |                |
| Caucasian        | 1076 (85.0%)    | 475 (83.3%)     | 130 (83.3%)     | 471 (87.2%)     | 0.59           |
| African American | 90 (7.1%)       | 46 (8.1%)       | 15 (9.6%)       | 29 (5.4%)       |                |
| Hispanic/Latino  | 35 (2.8%)       | 20 (3.5%)       | 5 (3.2%)        | 10 (1.9%)       |                |
| Asian            | 20 (1.6%)       | 11 (1.9%)       | 2 (1.3%)        | 7 (1.3%)        |                |
| American Indian  | 2 (0.2%)        | 1 (0.2%)        | 0 (0.0%)        | 1 (0.2%)        |                |
| Others           | 10 (0.8%)       | 4 (0.7%)        | 1 (0.6%)        | 5 (0.9%)        |                |
| Missing/Unknown  | 33 (2.6%)       | 13 (2.3%)       | 3 (1.9%)        | 17 (3.2%)       |                |
| Left ventricular ejection fraction (%) | 42 ± 17        | 25 ± 7          | 42 ± 2          | 59 ± 6          | <0.0001        |
| Diabetes mellitus | 309 (22.9%)    | 167 (27.9%)     | 29 (17.7%)      | 113 (19.3%)     | <0.001         |
| Hypertension     | 912 (67.7%)     | 425 (71.1%)     | 111 (67.7%)     | 376 (64.3%)     | 0.044          |
| Peripheral vascular disease | 21 (1.6%) | 13 (2.2%) | 3 (1.8%) | 5 (0.9%) | 0.18 |
| Hypercholesterolemia | 757 (56.2%) | 372 (62.2%) | 91 (55.5%) | 294 (50.3%) | <0.001 |
| Ischaemic heart disease | 388 (28.8%) | 244 (40.8%) | 37 (22.6%) | 107 (18.3%) | <0.0001 |
| Active smoking   | 89 (6.6%)       | 55 (9.2%)       | 8 (4.9%)        | 26 (4.4%)       | 0.003          |
| ACEi/ARB         | 772 (57.3%)     | 422 (70.6%)     | 108 (65.9%)     | 242 (41.4%)     | <0.0001        |
| Beta-blocker     | 1030 (76.5%)    | 527 (88.1%)     | 138 (84.2%)     | 365 (62.4%)     | <0.0001        |
| Aspirin          | 617 (45.8%)     | 303 (50.7%)     | 69 (42.1%)      | 245 (41.9%)     | 0.006          |
| Statin           | 655 (46.8%)     | 323 (54.0%)     | 80 (48.8%)      | 252 (43.1%)     | <0.001         |
| Digoxin          | 54 (4.0%)       | 40 (6.7%)       | 5 (3.1%)        | 9 (1.5%)        | <0.0001        |
| Loop diuretics/Metolazone | 849 (63.0%) | 403 (67.4%) | 89 (54.3%) | 357 (61.0%) | 0.004 |
| MRA              | 327 (24.3%)     | 214 (35.8%)     | 45 (27.4%)      | 68 (11.6%)      | <0.0001        |

ACEi/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist.

Values are mean ± SD or \(n\) (%).

\(^a\)Available in 1266/1347 patients.
Table 2 Cardiopulmonary exercise testing results, overall, and by left ventricular ejection fraction category

|                          | Entire cohort (n = 1347) | HFrEF (n = 598) | HfmrEF (n = 164) | HfPEF (n = 585) | P value |
|--------------------------|--------------------------|-----------------|------------------|-----------------|---------|
| VE/VCO2 slope            | 32.0 (27.9, 38.4)        | 33.8 (29.2, 41.8) | 30.0 (26.4, 44.5) | 31.0 (27.2, 36.8) | <0.001  |
| Peak VO2 (mL/kg/min)     | 15.0 ± 6.6               | 13.8 ± 5.3      | 16.0 ± 6.8       | 16.0 ± 7.5      | <0.001  |
| Peak VO2 < 14 mL/kg/min  | 721 (53.8%)              | 363 (60.9%)     | 73 (45.1%)       | 285 (49.0%)     | <0.001  |
| Peak RER                 | 1.16 ± 0.14              | 1.17 ± 0.14     | 1.16 ± 0.10      | 1.15 ± 0.14     | 0.005   |
| Resting heart rate (bpm) | 72.2 ± 14.0              | 73.8 ± 14.6     | 70.9 ± 12.5      | 70.8 ± 13.5     | <0.001  |
| Peak heart rate (bpm)    | 120.4 ± 28.0             | 117.5 ± 26.6    | 123.1 ± 27.9     | 122.7 ± 29.2    | 0.003   |
| Resting SBP (mmHg)       | 73.3 ± 11.0              | 72.4 ± 10.4     | 73.3 ± 11.2      | 74.1 ± 11.4     | 0.040   |
| Peak SBP (mmHg)          | 145.3 ± 31.5             | 132.7 ± 28.0    | 145.6 ± 25.2     | 158.2 ± 31.3    | <0.001  |
| Peak DBP (mmHg)          | 73.6 ± 12.5              | 71.6 ± 11.9     | 74.6 ± 12.5      | 75.3 ± 12.8     | <0.001  |
| Exercise duration (min)  | 7.4 ± 2.9                | 7.3 ± 2.8       | 7.9 ± 3.1        | 7.3 ± 2.9       | 0.05    |

bpm, beats per minute; DBP, diastolic blood pressure; HfmrEF, heart failure with mid-range ejection fraction; HfPEF, heart failure with preserved ejection; HFrEF, heart failure with reduced ejection fraction; METs, metabolic equivalents; RER, respiratory exchange ratio; SBP, systolic blood pressure; VE/VCO2, minute ventilation to carbon dioxide production ratio; VO2, oxygen uptake.

Values are mean ± SD, median (interquartile range) or n (%).

tients with HFrEF had a higher proportion with peak VO2 below 14 mL/kg/min (60.9% vs. 45.1% vs. 49.0%, P < 0.001) and achieved a statistically significantly lower peak VO2 (13.8 ± 5.3 vs. 16.0 ± 6.8 vs. 16.2 ± 7.5, P < 0.001; Table 2). Patients with HFrEF also had higher median VE/VCO2 slope [33.8 (IQR 29.2, 41.8) vs. 30.0 (IQR 26.4, 44.5) vs. 31.0 (27.2, 36.8), P < 0.001; Table 2]. In addition, patients with HFrEF had higher resting heart rate, lower peak heart rate, and lower systolic and diastolic blood pressures at rest and at peak exercise (Table 2). Compared with HfmrEF patients, patients with HfPEF had significantly higher resting and peak systolic blood pressures (Table 2).

VE/VCO2 slope category as a predictor of the 2 year composite endpoint

There were 201 composite events (65 deaths and 136 HF hospitalizations) over a median follow-up of 2.0 (1.9, 2.0) years (range: 6–730 days) from CPET (Table 3). Higher VE/VCO2 slope categories were associated with incremental 2 year cumulative incidences of the composite outcome within each HF category (Figure 1). Across the entire study cohort, compared with patients in VC-I, those in VC-II, III, and IV had over three-fold, five-fold, and eight-fold increased hazards of the primary composite endpoint (hazard ratio (HR) 3.12, 95% CI 1.86 to 5.26, P < 0.001; HR 5.47, 95% CI 3.20 to 9.35, P < 0.001; HR 8.21, 95% CI 4.75 to 14.18, P < 0.001, respectively; Table 4).

In patients with HFrEF (n = 598), there were 128 composite events within 2 years of CPET (Table 3). Compared with patients in VC-I, patients with HFrEF in VC-II, III, and IV demonstrated incremental risk of the primary composite endpoint (HR 2.82, 95% CI 1.40 to 5.68, P = 0.004; HR 5.09, 95% CI 2.55 to 10.19, P < 0.001; HR 6.02, 95% CI 2.93 to 12.38, P < 0.001, respectively; Table 4).

Among patients with HfmrEF (n = 164), there were 19 composite events within 2 years of CPET (Table 3). Among patients with HfmrEF, VC-III and IV demonstrated increased hazards of the primary composite endpoint compared with VC-I in both unadjusted and adjusted analyses (Tables 4 and S2). VC-II had a trend towards increased risk but did not achieve statistical significance in either unadjusted or adjusted analyses (Tables 4 and S2).

Fifty-four composite events occurred within 2 years of CPET in the HfPEF cohort (n = 585) (Table 3). As with HFrEF, each incremental VE/VCO2 slope category was associated with an increased hazard of the composite endpoint, even after adjusting for age and gender (Tables 4 and S2).

When examined as a continuous variable across the entire cohort, increasing VE/VCO2 slope was associated with a progressive increase in the risk of the 2 year composite outcome (Figure 2).

Table 3 Study outcome for the entire cohort and left ventricular ejection fraction subgroups

|                          | Entire cohort (n = 1347) | HFrEF (n = 598) | HfmrEF (n = 164) | HfPEF (n = 585) |
|--------------------------|--------------------------|-----------------|------------------|-----------------|
| Follow-up time* (years)  | 2.0 (1.9, 2.0)           | 2.0 (2.0, 2.0)  | 2.0 (2.0, 2.0)   | 2.0 (1.8, 2.0)  |
| Range, days              | 6–730                    | 6–730           | 13–730           | 8–730           |
| Deaths + HF hospitalizations, n | 201                    | 128             | 19               | 54              |
| Deaths, n               | 65                       | 41              | 6                | 18              |
| HF hospitalizations, n   | 136                      | 87              | 13               | 36              |

HF, heart failure; HfmrEF, heart failure with mid-range ejection fraction; HfPEF, heart failure with preserved ejection; HFrEF, heart failure with reduced ejection fraction.

*Values are expressed as median (interquartile range).
Figure 1  Cumulative incidence of 2 year composite outcome (death and HF admissions) across VE/VCO₂ slope categories for (A) all cohorts, (B) HFrEF cohort over time, (C) HFmrEF cohort over time, and (D) HFpEF cohort over time. HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; VC, ventilatory efficiency category.

Table 4  Association between VE/VCO₂ slope categories and death + HF hospitalization across HF LVEF categories

|                      | Entire cohort (n = 1347) | HFrEF (n = 598) | HFmrEF (n = 164) | HFrEF (n = 585) |
|----------------------|--------------------------|----------------|------------------|-----------------|
|                      | Adjusted HR<sup>a</sup> (95% CI) | P value | Adjusted HR<sup>a</sup> (95% CI) | P value | Adjusted HR<sup>a</sup> (95% CI) | P value | Adjusted HR<sup>a</sup> (95% CI) | P value |
| VC-I                 | 1.0                      | 1.0          | 1.0              | 1.0            | 1.0              | 1.0          | 1.0              | 1.0          |
| VC-II                | 3.12 (1.86, 5.26)        | <0.0001      | 2.82 (1.40, 5.68) | 0.004          | 3.98 (0.82, 19.23) | 0.09    | 2.67 (1.11, 6.40) | 0.028 |
| VC-III               | 5.47 (3.20, 9.35)        | <0.0001      | 5.09 (2.55, 10.19) | <0.0001       | 8.72 (1.67, 45.60) | 0.010  | 2.96 (1.13, 7.78) | 0.027 |
| VC-IV                | 8.21 (4.75, 14.18)       | <0.0001      | 6.02 (2.93, 12.38) | <0.0001       | 10.55 (2.03, 54.79) | 0.005  | 8.68 (3.52, 12.40) | <0.0001 |

CI, confidence interval; HF, heart failure; HFmrEF, HF with mid-range ejection fraction; HFrEF, HF with preserved ejection fraction; HFrEF, HF with reduced ejection fraction; HR, hazard ratio, VC, ventilatory category; VE/VCO₂, minute ventilation to carbon dioxide production ratio.

VC-I: VE/VCO₂ slope ≤ 29, VC-II: 29 < VE/VCO₂ slope < 36, VC-III: 36 ≤ VE/VCO₂ slope < 45, VC-IV: VE/VCO₂ slope ≥ 45.

<sup>a</sup>Adjusted for age (continuous) and gender.
Receiver operating characteristic analysis

Receiver operating characteristic analysis demonstrated that a threshold VE/VCO₂ slope > 36, which is commonly employed in clinical practice, was more specific but less sensitive for the primary composite endpoint when applied to the HFmrEF and HFpEF cohorts compared with the HFrEF cohort (Table 5). Alternatively, a lower VE/VCO₂ slope cut-point of 29 was associated with higher sensitivity (>85.0% in all three categories) at the cost of lower specificity across all HF categories (Table 5). These cut-points were then independently validated in our cohort (Figure 3). We compared the predictive value of peak VO₂, VE/VCO₂ slope, and the combination of peak VO₂ and VE/VCO₂ slope for each LVEF category. Our
Table 5  Sensitivities and specificities of various VE/VCO₂ slope cut-points among HF groups, defined by LVEF

| VE/VCO₂ slope ≥ 36 | Sensitivity (95% CI) | Specificity (95% CI) |
|--------------------|---------------------|---------------------|
| HFrEF              | 61.1% (52.6%, 70.7%)| 64.7% (60.5%, 69.2%)|
| HFmrEF             | 41.6% (20.9%, 70.3%)| 82.1% (75.7%, 88.2%)|
| HfEF               | 47.0% (33.2%, 62.9%)| 74.2% (70.5%, 77.9%)|

| VE/VCO₂ slope ≥ 29 | Sensitivity (95% CI) | Specificity (95% CI) |
|--------------------|---------------------|---------------------|
| HFrEF              | 90.5% (86.0%, 95.0%)| 28.4% (24.3%, 32.6%)|
| HFmrEF             | 87.9% (67.1%, 100.0%)| 46.1% (38.0%, 55.7%)|
| HFpEF              | 85.0% (75.0%, 93.8%)| 39.2% (34.9%, 43.3%)|

CI, confidence interval; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with mid-range ejection fraction; HfEF, heart failure with preserved ejection fraction; VE/VCO₂, minute ventilation to carbon dioxide production ratio.

Discussion

In this retrospective cohort study, we explored the prognostic value of a multilevel classification system for VE/VCO₂ slope to predict the 2 year composite outcome of all-cause mortality and HF hospitalization across HF cohorts defined by LVEF. Incremental decreases in ventilatory efficiency were associated with an increased risk of the composite outcome in patients with HFrEF, HFmrEF, and HFpEF, respectively. The currently used cut-point of VE/VCO₂ slope ≥ 36 was prognostic across all HF categories but was associated with lower sensitivity for predicting adverse outcomes in the HFmrEF or HFpEF cohorts compared with patients with HFrEF. Furthermore, among patients with HFrEF or HFpEF, a VE/VCO₂ slope between 29 and 36, currently considered borderline abnormal in clinical practice, was associated with a greater than two-fold risk of the composite outcome, after adjusting for age and gender. Thus, our data suggest that relying on a single VE/VCO₂ slope threshold of ≥36 in HF patients may under-acknowledge risk in patients with VE/VCO₂ slopes in this ‘borderline abnormal’ category who might otherwise benefit from closer follow-up and intensification of medical therapy.

Studies examining VE/VCO₂ slope as a predictor of adverse outcomes have largely focused on patients with HFrEF.4–7,15–21 In patients with HFrEF, every unit increase in VE/VCO₂ slope has been associated with a 4–10% increase in the risk of all-cause mortality, CV death, or cardiac
transplantation.\textsuperscript{15,16,18,20} VE/VCO\textsubscript{2} slope has received comparatively less attention in patients with HFP EF and HFmrEF.\textsuperscript{9,10,20–22} One small study (n = 173) failed to establish a significant association between increasing VE/VCO\textsubscript{2} slope and the risk of death or cardiac transplantation in patients with HFP EF.\textsuperscript{3} However, another study of 88 patients with LVEF $\geq$ 45% reported an almost two-fold increased risk of all-cause mortality with each 10 unit increase in VE/VCO\textsubscript{2} slope.\textsuperscript{21} Similar results were seen in a large retrospective study of 493 patients with LVEF $\geq$ 50% where each unit increase in VE/VCO\textsubscript{2} slope was associated with a 1.5-fold increase in the risk of CV hospitalization and death.\textsuperscript{22} Data in HFmrEF are more limited, and a single study of 144 patients reported a 12% increase in the combined risk of LVAD implantation, cardiac transplantation, or all-cause mortality per unit increase in VE/VCO\textsubscript{2} slope.\textsuperscript{20} A recent analysis of 269 patients with HF across a range of LVEF similarly showed that increasing VE/VCO\textsubscript{2} slope categories were associated with an increased risk of HF hospitalization and death. However, this analysis did not assess the predictive value of different VE/VCO\textsubscript{2} slope categories in patients with HFrEF, HFmrEF, and HFP EF.\textsuperscript{23} Our study adds to this literature and advances our understanding of the prognostic value of VE/VCO\textsubscript{2} slope in patients with HFmrEF and HFP EF, reinforcing the utility of this parameter in these cohorts.

In current clinical practice, VE/VCO\textsubscript{2} slope is categorized as normal/abnormal in a dichotomous manner across a cut-point of 36. This binary approach fails to provide optimal refinement of risk prediction. Prior studies attempting to categorize VE/VCO\textsubscript{2} slope as a multilevel variable have shown value in patients with HFrEF but have conflicting results in patients with HFP EF. No prior studies have evaluated VE/VCO\textsubscript{2} slope as a multilevel variable in HFmrEF. Francis et al. divided 303 patients with mean LVEF 25 $\pm$ 11% into four quartiles based on VE/VCO\textsubscript{2} slope and demonstrated that patients in higher quartiles had increasing risk of 2 year mortality (3%, 17%, 26%, and 49% from lowest to highest quartiles, respectively).\textsuperscript{24} In a cohort of 663 patients with HFrEF, Ferreira et al. categorized VE/VCO\textsubscript{2} slope into five-unit increments above 30 and found worse survival across ascending VE/VCO\textsubscript{2} slope categories.\textsuperscript{25} Similarly, Arena et al. divided 448 patients with either systolic or diastolic HF into four VE/VCO\textsubscript{2} slope categories and observed that higher VE/VCO\textsubscript{2} slope categories were associated with a higher likelihood of death, cardiac transplantation, or LVAD implantation; in subgroup analyses, these results held true in patients with HFrEF (LVEF $\leq$ 40%) but not in those with EF $>$ 40%.\textsuperscript{3} In contrast, two studies have shown incremental risk with increasing VE/VCO\textsubscript{2} slope in patients with HFP EF. A study of 88 patients with HFP EF reported a 1.44-fold and 3.57-fold increased risk of all-cause mortality among those in the middle and highest tertiles for VE/VCO\textsubscript{2} slope compared with those in the lowest tertile, respectively.\textsuperscript{21} A recent study of 483 patients with HFP EF (LVEF $\geq$ 50%) similarly demonstrated that patients in the middle and highest tertiles for VE/VCO\textsubscript{2} slope had a 1.72-fold and 2.44-fold increased risk of CV hospitalization and death compared with those in the lowest tertile.\textsuperscript{22} A study of 269 subjects showed a 1.4-fold increase risk of HF hospitalization and death with increasing VE/VCO\textsubscript{2} slope categories across a range of LVEF.\textsuperscript{23} Our study builds upon the available data and highlights an opportunity for risk refinement by considering VE/VCO\textsubscript{2} slope as a multilevel rather than dichotomous variable across all types of HF defined by LVEF.

Our findings demonstrate that the current VE/VCO\textsubscript{2} slope cut-point of $\sim$36 is less sensitive for predicting risk in patients with HFmrEF and HFP EF compared with those with HFrEF. Thus, our data caution against the uniform application of this cut-point in HFmrEF and HFP EF patients and larger studies are needed to identify optimal VE/VCO\textsubscript{2} slope thresholds in these cohorts. Our data also highlight that a borderline VE/VCO\textsubscript{2} slope of 29–36 manifests significantly increased risk in patients with HFrEF and HFP EF relative to a normal VE/VCO\textsubscript{2} slope of less than 29. While not statistically significant, a similar trend for increased risk was seen in patients with HFmrEF. This increased risk should be considered when managing patients with VE/VCO\textsubscript{2} slope of 29–36.

Our study has several limitations inherent to the retrospective study design. These include the selection bias of studying patients with HF clinically referred for CPET, as reflected by the relatively younger age of patients with HFP EF in this study compared with community studies. The small number of events (n = 19) in the HFmrEF cohort may have limited
the power to detect a significant predictive value for VE/VCO₂ slope of 29–36. Importantly, we are unable to account for the effect of non-HF comorbidities that influence VE/VCO₂ slope, such as non-group II pulmonary hypertension or chronic obstructive pulmonary disease, on risk of adverse events across different HF categories. HFrEF was defined as a chart diagnosis of HF or documented use of loop diuretics/metolazone plus EF ≥ 50% defined by echocardiography or cardiac magnetic resonance imaging. We did not have data on natriuretic peptides or detailed echocardiogram characteristics required to make an accurate diagnosis of HFrEF. Furthermore, we acknowledge that HFrEF is a heterogeneous disease entity. However, given the nature of retrospective data, we were unable to define the particular aetiology of HFrEF for each subject in our study. Additionally, our cohort was relatively young, and our findings may not be applicable to those with age-associated HFrEF.

In conclusion, the current clinical practice of utilizing a single threshold for defining an abnormal VE/VCO₂ slope in all patients with HF should be reconsidered. This approach is limited by differences in sensitivity for risk prediction across different HF categories defined by LVEF. Additionally, we demonstrate that a multilevel, rather than dichotomous, approach to VE/VCO₂ slope interpretation further refines risk prediction across all categories of HF defined by LVEF. Specifically, in patients with HFrEF or HFrEF, a VE/VCO₂ slope between 29 and 36, currently considered borderline, is associated with increased risk and should be considered when managing patients in clinical practice. Larger studies are needed to develop more granular systems for the interpretation of VE/VCO₂ slope within each of the HF categories, defined by LVEF, to maximally inform risk stratification and optimize patient management.

Conflict of interest

Outside the submitted work, J.D.G. received research support from Amgen, Inc. A.N. is a consultant for Takeda Oncology, AstraZeneca and Boehringer Ingelheim and receives research support from Amgen, Inc. A.O. has received research support from and serves on an Independent Data Monitoring Committee for Actelion/Johnson and Johnson. J.G., J.C., R.C., C.B., J.H., M.R.M., B.A.M., and M.D.C. have no conflicts relevant to the manuscript to disclose.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. CONSORT diagram of the study cohort.
Figure S2A. Time-dependent Receiver Operating Characteristic (ROC) Curves describing the ability of VE/VCO₂ slope, peak VO₂ and the combination of VE/VCO₂ slope and peak VO₂ to predict the two-year composite outcome of all-cause mortality and HF hospitalizations in patients with HFrEF.
Figure S2B. Time-dependent Receiver Operating Characteristic (ROC) Curves describing the ability of VE/VCO₂ slope, peak VO₂ and the combination of VE/VCO₂ slope and peak VO₂ to predict the two-year composite outcome of all-cause mortality and HF hospitalizations in patients with HFmrEF.
Figure S2C. Time-dependent Receiver Operating Characteristic (ROC) Curves describing the ability of VE/VCO₂ slope, peak VO₂ and the combination of VE/VCO₂ slope and peak VO₂ to predict the two-year composite outcome of all-cause mortality and HF hospitalizations in patients with HFrEF.

Table S1. Definition of heart failure admission.
Table S2. Unadjusted association Between VE/VCO₂ Slope Categories and Death + HF Hospitalization Across HF Categories.

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