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ORIGINAL RESEARCH

Revisiting and Implementing the Weber and Ventilatory Functional Classifications in Heart Failure by Cardiopulmonary Imaging Phenotyping

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BACKGROUND: In heart failure, the exercise gas exchange Weber (A to D) and ventilatory classifications (VC-1 to VC-4) historically define disease severity and prognosis. However, their applications in the modern heart failure population of any left ventricular ejection fraction combined with hemodynamics are undefined. We aimed at revisiting and implementing these classifications by cardiopulmonary exercise testing imaging.

METHODS AND RESULTS: 269 patients with heart failure with reduced (n=105), mid-range (n=88) and preserved (n=76) ejection fraction underwent cardiopulmonary exercise testing imaging, primarily assessing the cardiac output (CO), mitral regurgitation, and mean pulmonary arterial pressure (mPAP)/CO slope. Within both classes, a progressively lower exercise CO, higher mPAP/CO slopes, and mitral regurgitation ($P<0.01$ all) were observed. After adjustment for age and sex, Cox proportional hazard regression analyses showed that Weber (hazard ratio [HR], 2.9; 95% CI, 1.8–4.7; $P<0.001$) and ventilatory classes (HR, 1.4; 95% CI, 1.1–2.0; $P=0.017$) were independently associated with outcome. The best stratification was observed when combining Weber (A/B or C/D) with severe ventilation inefficiency (VC-4) (HR, 2.7; 95% CI, 1.6–4.8; $P<0.001$). At multivariable analysis the best hemodynamic determinants of peak oxygen consumption and ventilation to carbon dioxide production slope were CO (β-coefficient, 0.72±0.16; $P<0.001$) and mPAP/CO slope (β-coefficient, 0.72±0.16; $P<0.001$), respectively.

CONCLUSIONS: In the contemporary heart failure population, the Weber and ventilatory classifications maintain their prognostic ability, especially when combined. Exercise CO and mPAP/CO slope are the best predictors of peak oxygen consumption and ventilation to carbon dioxide production slope classifications representing the main targets of interventions to impact functional class and, likely, event rate.

Key Words: exercise gas exchange ■ peak VO_2 ■ VE/VCO_2 slope

In heart failure (HF), the high clinical and prognostic value of functional evaluation by exercise gas exchange is well established.[1,2] Pioneer studies by Weber et al[3] and Mancini et al[4] introduced and proposed the use of cardiopulmonary exercise testing (CPET) in daily practice and the oxygen consumption (VO_2) at peak exercise became then a measure of standard for staging the severity of the disease, unmasking the underlying pathophysiology, and addressing the optimal timing for advanced treatment. In their landmark paper of 1982, Weber et al[3] proposed a classification based on 4 different categories of peak VO_2, which paved the way to a large amount of evidence and advancements in the care setting and risk stratification of patients with HF.[5]

Starting in the late 1990s, an additional CPET-derived variable, that is, the rate of ventilation (VE) to carbon dioxide production (VCO_2) slope, was

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CLINICAL PERSPECTIVE

What Is New?

- In heart failure, the exercise gas exchange Weber (A to D) and ventilatory classifications (VC-1 to VC-4) historically have been part of defining disease severity and prognosis.
- In 269 patients with heart failure with reduced (n=105), midrange (n=88), and preserved (n=76) ejection fraction, we revisited and implemented these classifications by cardiopulmonary exercise testing.
- The best stratification was observed when combining Weber (A/B or C/D) classes with VC-4 and the best hemodynamic determinants of peak oxygen consumption and ventilation to carbon dioxide production slope were cardiac output and mean pulmonary arterial pressure/cardiac output, respectively.

What Are the Clinical Implications?

- In the contemporary HF population, the Weber and ventilatory classifications maintain their prognostic ability, especially when combined.
- Exercise cardiac output and mean pulmonary arterial pressure/cardiac output slope, as the best predictors of peak oxygen consumption and ventilation to carbon dioxide production slope classifications, may represent targets for interventions to impact functional class and, possibly, event rate.

Nonstandard Abbreviations and Acronyms

CO	cardiac output
CPET	cardiopulmonary exercise testing
EOV	exercise oscillatory ventilation
HFpEF	heart failure with preserved left ventricular ejection fraction
HFrEF	heart failure with reduced left ventricular ejection fraction
mPAP	mean pulmonary arterial pressure
PASP	pulmonary artery systolic pressure
TAPSE	tricuspid annular plane systolic excursion
VC	ventilatory classification
ΔWR	changes in work rate

repeatedly found to be more predictive than peak VO_2.[6] Advantages over peak VO_2 were confirmed by a preserved prognostic ability even in patients with a near-normal peak VO_2 (≥18 mL/min per kg)[7] and by the high event-rate prediction also at submaximal stages of exercise being the relationship independent of the maximal workload.[8] Following the mounting evidence over the years, in 2007 Arena et al[9] proposed the ventilatory classification (VC), that is, 4 classes of VE/VCO_2 slope, as an integrative way to optimize the CPET-derived risk stratification in HF.

Nowadays, either variable is used in isolation or more often in combination under score's format for prognostic purposes[10] and as end point in pharmacological[11,12] and interventional trials.[13,14]

Although many studies have focused on the complex mechanisms and pathways involved in the limitations to O_2 uptake[15–17] and the perturbed ventilatory response,[18,19] a thorough exercise phenotyping by CPET imaging and hemodynamic assessment to establish the value of these classifications in a contemporary population of HF with preserved (HFpEF), midrange, and reduced (HFrEF) left ventricular ejection fraction is lacking.

Accordingly, we aimed at revisiting and implementing the use of the Weber and ventilatory (VC) classifications in a comprehensive cohort of patients with HF with a 2-fold aim: (1) to provide some up-to-date perspectives and implications in terms of prognostic prediction and (2) to identify the hemodynamic variables that better define exercise O_2 uptake and ventilatory efficiency.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Population

Consecutive patients referred to the Cardiology University Department at San Donato HF Unit for functional assessment between January 2013 and February 2019 were considered for study recruitment. The population was composed of 269 patients with HF distributed as follows: HFrEF, n=105; HF with mid-range ejection fraction, n=88; and HFpEF, n=76. They were tested by CPET imaging with echo evaluation of systolic and diastolic left ventricular (LV) function, left atrial (LA) dynamics by speckle tracking analysis and right ventricular (RV) function evaluation. Exclusion criteria consisted of recent myocardial infarction (<3 months), unstable angina, evidence of inducible myocardial ischemia, atrial fibrillation, peripheral artery disease, significant anemia (hemoglobin <10 g/dL), and respiratory diseases more than a moderate degree. Patients on pacing and with poor echocardiographic image quality for LA speckle tracking analysis during exercise were excluded from the final analysis. All patients signed

2 informed consents, for the test execution for research use as approved by our local ethical committee. Therapy was maintained during evaluation.

Rest and Exercise Echocardiography

A complete echocardiographic evaluation was performed using a Philips IE33 at rest, recording standard images to assess LV systolic, diastolic, and valvular function. Our exercise echocardiographic evaluation has been described previously.[19,20] LA dynamics was evaluated by measuring LA strain according to the American Society of Echocardiography/European Association of Cardiovascular Imaging Guidelines,[21] the first for assessing reservoir function and the second for booster pump function. These measurements were derived from the apical 4-chamber and 2-chamber views and using QRS onset as the reference point. During exercise and in the recovery period, LA strain and LA strain rate were obtained by averaging all segment strain values from the apical 4-chamber views. LV diastolic function was assessed by early (E) to late (A) mitral Doppler wave velocity and LV filling pressure by the ratio between E and early tissue Doppler velocity wave (e′). LA stiffness was calculated as the ratio between LA-strain and E/e′. During exercise, the same projections were registered every 2 minutes, especially when a respiratory exchange ratio value of >1 was reached. Loop registration of at least 5 seconds was used to overcome the expected decrease in acoustic quality caused by hyperventilation. We defined the peak state as the period from the last 30 seconds of peak exercise to the first minute of the cool-down period. Subsequent images were categorized as the recovery period. All echocardiographic parameters were obtained according to current indications, as previously reported.[20] Data recordings were performed by 2 cardiologists (T.S. and F.B.) with a long-standing (>10 years) experience on exercise echo stress. The analysis of LA dynamics was performed offline by 1 cardiologist (T.S.), who was blinded to the clinical characteristics of the subjects using 2-dimensional speckle tracking echocardiography with the ultrasound software package QLAB version 10.4 (Philips, Amsterdam, the Netherlands). The stroke volume was measured applying the equation stroke volume $=\mathrm{VTI}_{\mathrm{LVOT}}\times\mathrm{CSA}_{\mathrm{LVOT}}$, where $\mathrm{VTI}_{\mathrm{LVOT}}$ is the velocity time integral of pulsatile Doppler obtained at the level of LV outflow tract (LVOT) and $\mathrm{CSA}_{\mathrm{LVOT}}$ is the cross-sectional area of LVOT, determined using the circumference area formula. Cardiac output (CO) was obtained as stroke volume×heart rate, both at rest and at peak exercise. Pulmonary artery systolic pressure (PASP) was estimated measuring the peak velocity of transtricuspid continuous Doppler and calculating the gradient as 4×(peak velocity); right atrial pressure during exercise was estimated as a fixed value of 10 mm Hg, as previously proposed by other authors.[22] mPAP was calculated using the formula: 0.61×PASP+2. Longitudinal systolic function of the right ventricle was measured by tricuspid annular plane systolic excursion (TAPSE) from the 4-chamber view. Finally, to assess the severity of the RV to pulmonary circulation uncoupling, we calculated the mean pulmonary arterial pressure (mPAP)/CO relationship and the TAPSE/PASP ratio, both at rest and at peak exercise, as previously described.[23,24]

Cardiopulmonary Exercise Test

In all subjects, a symptom-limited CPET was performed on cycle ergometer for all subjects. Incremental ramp protocols were designed to obtain a standard of exercise. To facilitate simultaneous echocardiographic assessment, we limited the ramp steep to a maximum of 15 W per minute. Ventilatory expired gas analysis was performed using a metabolic cart (Vmax; Sensormedics, Yorba Linda, CA). Standard 12-lead ECG and blood pressure were obtained at rest, each minute during exercise, and for a period ≥4 minutes during the recovery phase. Baseline metabolic evaluation was performed during a 1-minute rest period before exercise and during active cool-down period for ≥1 minute. VE, VO_2, and VCO_2 were acquired breath-by-breath and averaged for 10 seconds. Peak VO_2 and peak respiratory exchange ratio were expressed as the averaged sample obtained during the final 20 seconds. Exercise ventilation efficiency was addressed by the VE increase for a given VCO_2 slope and calculated via least squares linear regression (y=mx+b; m is slope). Changes (Δ) in VO_2 over changes in work rate (ΔWR) flattening and exercise oscillatory ventilation (EOV) were defined as detailed in the European Association for Cardiovascular Prevention & Rehabilitation/American Heart Association CPET Consensus Statement.[5]

Statistical Analysis

Data are presented as the mean±SD, numbers (percentage) or median (interquartile range) as appropriate. Group differences were evaluated using the Student *t* test for normally distributed continuous variables, Mann-Whitney *U* tests for non–normally distributed continuous variables, and the chi-square or Fisher exact tests for categorical variables. One-way analysis of variance or Kruskal–Wallis tests were used to compare >2 groups. When a significant difference was found, post hoc testing with Bonferroni comparisons for identified specific group differences was used. Pearson or Spearman correlation coefficients were used to examine the relationship between continuous variables. Cumulative event-free survival estimates were calculated using the Kaplan-Meier method. Log-rank test was used for comparing the curves. Associations between CPET and echocardiographic parameters were determined using logistic regression analysis. Choice of covariates to incorporate in the univariate and multivariate models was based on the main factors known to be related to exercise performance. Associations between CPET parameters and clinical outcome were determined using Cox proportional hazards analysis in the univariate and multivariate models after adjusting age and sex. The interaction between the combined Weber and VC stratification versus EOV, $\Delta\text{VO}_2/\Delta\text{WR}$ flattening and peak mitral regurgitation, that are, the variables well recognized to be associated with exercise performance, were assessed by Cox proportional hazard regression analyses for clinical outcomes. Standardized β-coefficients rather than regular β-coefficients were reported. For all tests, a *P* value of <0.05 (2-sided) was considered significant. Data were analyzed using the open-source statistical software R version 3.3.2 (R Foundation for Statistical Computing, www.R-project.org).

RESULTS

Patient Population

Table 1 reports the clinical characteristics and therapy distribution of the entire population (n=269) and 4 groups according to Weber classes (Weber class A, peak VO_2 >20 mL/kg per minute, n=35; class B, peak VO_2 16–20 mL/kg per minute, n=65; class C, peak VO_2 10–16 mL/kg per minute, n=124; and class D, peak VO_2 ≤10 mL/kg per minute, n=45). There were significant differences in age, body mass index, prevalence of hypertension, diabetes mellitus, and dyslipidemia, and the prescription of beta-blockers, loop diuretics, aldosterone blockers, ivabradine, statins, and nitrates among 4 groups. Significant higher rates of hypertension, diabetes mellitus, and dyslipidemia were observed from Weber classes A to D. Especially, HFrEF phenotype was more represented in Weber class D.

Table 1. Clinical Characteristics and Therapy Distribution of the Entire Population and 4 Groups According to Weber Classes

	All (n=269)	Weber Class A (n=35)	Weber Class B (n=65)	Weber Class C (n=124)	Weber Class D (n=45)	*P* Value
Age, y	64.6±13.3	49.7±12.7	61.9±12.6	68.2±10.9	69.9±11.6	<0.001
Male sex						
Sex, %	59	69	72	61	60	0.401
Body mass index, kg/m^2	26.6±4.5	23.5±3.2	25.9±3.3	27.4±4.5	27.5±5.5	<0.001
Systolic blood pressure, mm Hg	124±20	120±13	124±21	125±21	121±18	0.442
Heart rate, beats/min	69±12	66±13	71±14	69±12	70±10	0.425
Hypertension, %	66	37	62	73	78	<0.001
Diabetes mellitus, %	26	6	20	27	49	<0.001
Dyslipidemia, %	57	26	55	65	64	<0.001
Current or ex-smoker, %	42	40	48	39	40	0.713
Etiology						
HFrEF, %	45	11	39	48	71	<0.001
HFmrEF, %	20	23	23	20	16	0.778
HFpEF, %	16	3	15	21	13	0.055
Therapy						
ACE inhibitors or ARB, %	66	54	74	40	30	<0.01
β blockers, %	73	46	68	80	80	<0.001
Sacubitril/Valsartan, %	30	25	25	60	65	0.03
Calcium channel blockers, %	11	6	8	13	16	0.362
Loop diuretics, %	64	26	52	72	91	<0.001
Aldosterone blockers, %	39	11	31	49	47	<0.001
Ivabradine, %	7	0	8	4	20	0.001
Statins, %	59	29	54	65	73	<0.001
Nitrates, %	8	0	6	8	18	<0.001

ACE indicates angiotensin converting enzyme; ARB, angiotensin receptor blockers; HFmrEF, heart failure with midrange ejection fraction; HFpEF, heart failure with preserved ejection fraction; and HFrEF, heart failure with reduced ejection fraction.

A progressive class-dependent impairment in exercise ventilatory efficiency and higher rate of $\Delta VO_2/\Delta WR$ flattening pattern and EOV was seen from A to D (Table 2). Imaging analysis demonstrated that LV mass, dimensions, E/e′ LA volume index, LA stiffness, mitral regurgitation degree at rest and at peak exercise, PASP at rest and during exercise, and mPAP/CO slope were progressively higher from Weber classes A through D. Conversely, left ventricular ejection fraction (LVEF), peak CO, peak cardiac power output, LA strain at rest and during exercise, TAPSE at rest and at peak exercise, TAPSE/PASP at rest and during exercise, and RV fractional area at rest and at peak exercise were progressively reduced (Table 2).

Patients were also divided into 4 subsets according to the VC classes: VC-1, VE/VCO_2 slope <30, n=143; VC-2, VE/VCO_2 slope 30 to 36, n=73; VC-3, VE/VCO_2 slope 36 to 45, n=35; and VC-4, VE/VCO_2 slope ≥45, n=18 (Table 3). There were significant differences in age, sex, and prescription of renin-angiotensin system inhibitors, loop diuretics, sacubitril/valsartan, aldosterone blockers, statins, and nitrates among 4 groups. No differences in the prevalence of comorbidities were observed. HFrEF was prevalent in VC class 4. Exercise gas exchange analysis documented a progressively worse performance (peak VO_2, VO_2 percent predicted), a higher rate of VO_2/WR flattening pattern, and EOV from VC-1 to VC-4 (Table 4). Imaging analysis demonstrated that LV dimensions, mass, E/e′ LA volume index, LA stiffness, mitral regurgitation degree at rest and peak exercise, peak systolic PASP at rest and during exercise, and mPAP/CO relationship were progressively higher from classes VC-1 to VC-4. Conversely, LVEF, peak CO, peak cardiac power output, LVEF, LA strain at rest and during exercise, TAPSE at rest and peak exercise, TAPSE/PASP at rest and

Table 2. CPET and Exercise Echocardiographic Variable in 4 Groups According to Weber Classes

	All (n=269)	Weber Class A (n=35)	Weber Class B (n=65)	Weber Class C (n=124)	Weber Class D (n=45)	*P* Value
Peak VO_2, mL/kg per min	15.0±5.6	26.1±4.8	17.6±1.1	12.8±1.7	8.6±0.9	…
Percent predicted peak VO_2, %	63±21	86±22	72±21	58±14	42±12	<0.001
VE/VCO_2 slope	31.2±7.9	26.5±2.5	28.8±5.1	31.4±7.1	38.1±10.9	<0.001
EOV, %	32	11	29	32	56	<0.001
$\Delta VO_2/\Delta WR$ flattening, %	16	0	2	20	37	<0.001
LV mass index at rest, g/m^2	121±38	94±27	117±33	125±41	138±35	<0.001
LV end-diastolic volume index at rest, mL/m^2	75±33	62±22	72±30	75±33	87±39	0.006
E/e′ at rest	16.5±10.5	8.3±2.5	13.4±6.2	17.7±11.1	23.6±11.8	<0.001
LV ejection fraction at rest, %	44±16	56±14	46±16	44±15	34±13	<0.001
Peak LV cardiac output, L/min	6.8±2.5	9.8±3.1	7.6±1.9	6.3±1.7	4.6±1.5	<0.001
Peak cardiac power output, mm Hg L/min	1.67±0.72	2.53±0.94	1.92±0.57	1.51±0.47	1.01±0.42	<0.001
Mitral regurgitation ≥2 at rest, %	30	6	15	33	62	<0.001
Peak mitral regurgitation ≥2, %	42	6	31	48	71	<0.001
Left atrial volume index at rest, mL/m^2	40.4±21.6	27.0±12.7	34.9±14.6	41.9±19.9	54.5±30.0	<0.001
Left atrial stiffness at rest	0.56 (0.28–1.57)	0.20 (0.17–0.31)	0.51 (0.27–1.00)	0.69 (0.34–1.75)	1.57 (0.77–3.09)	<0.001
Abnormal left atrial stiffness, %	51	6	45	55	84	<0.001
Left atrial strain at rest, %	24.0±13.2	37.3±12.3	25.3±11.2	22.3±12.4	16.5±11.0	<0.001
Left atrial strain during exercise, %	24.7±14.8	39.3±14.5	27.0±13.9	22.4±13.3	16.4±11.8	<0.001
Mean PAP/cardiac output slope, mm Hg/L per min	3.9 (2.5–7.3)	2.4 (1.6–2.9)	3.0 (1.8–4.7)	4.0 (2.9–7.3)	8.3 (4.8–17.0)	<0.001
Systolic PAP at rest, mm Hg	33±14	26±5	29±9	34±14	39±16	<0.001
Peak systolic PAP, mm Hg	53±14	44±9	49±13	54±14	57±13	<0.001
TAPSE at rest, mm	19.3±4.8	21.6±3.6	20.1±4.4	19.6±4.7	15.4±4.4	<0.001
Peak TAPSE, mm	21.8±5.7	26.6±3.9	22.9±4.5	21.6±5.6	17.0±5.3	<0.001
TAPSE/systolic PAP at rest, mm/mm Hg	0.67±0.29	0.88±0.22	0.78±0.31	0.64±0.26	0.45±0.21	<0.001
Peak TAPSE/systolic PAP, mm/mm Hg	0.45±0.22	0.63±0.22	0.56±0.26	0.43±0.17	0.31±0.13	<0.001
RV fractional area change at rest, %	45±12	48±8	46±11	46±11	37±15	<0.001
Peak RV fractional area change, %	42±13	49±8	48±13	42±12	34±15	<0.001

CPET indicates cardiopulmonary exercise test; E/e′, the ratio of the mitral peak velocity of the early filling (E) wave to early diastolic mitral annular velocity (e′); EOV, exercise oscillatory ventilation; LV, left ventricular; PAP, pulmonary artery pressure; RV, right ventricular; TAPSE, tricuspid annual plane systolic excursion; VE/VCO_2, ventilation over CO_2; and $\Delta VO_2/\Delta WR$, Δ oxygen consumption/Δ work rate.

Table 3. Baseline Characteristics in 4 Groups According to Ventilatory Classes

	Ventilatory Class 1 (n=143)	Ventilatory Class 2 (n=73)	Ventilatory Class 3 (n=35)	Ventilatory Class 4 (n=18)	*P* Value
Age, y	60.9±13.7	68.0±12.7	69.3±10.7	70.2±8.0	<0.001
Male sex, %	59	66	80	72	0.122
Body mass index, kg/m^2	27.0±4.8	26.6±4.0	25.6±3.8	24.5±3.9	0.067
Systolic blood pressure, mm Hg	126±19	121±21	118±19	124±15	0.085
Heart rate, beats/min	69±13	68±11	70±10	74±11	0.423
Hypertension, %	62	68	74	83	0.206
Diabetes mellitus, %	20	35	27	39	0.067
Dyslipidemia, %	53	64	71	44	0.098
Current or ex-smoker, %	40	42	41	56	0.648
Etiology					
HFrEF, %	30	58	63	72	<0.001
HFmrEF, %	18	22	23	28	0.675
HFpEF, %	21	12	11	0	0.06
Therapy					
ACE inhibitors or ARB, %	67	74	53	35	<0.01
β blockers, %	67	78	85	72	0.110
Sacubitril/Valsartan, %	20	30	50	75	0.02
Calcium channel blockers, %	13	13	3	6	0.298
Loop diuretics, %	53	68	85	100	<0.001
Aldosterone blockers, %	31	47	44	61	0.019
Ivabradine, %	6	6	9	22	0.069
Statins, %	48	71	71	78	0.001
Nitrates, %	5	8	15	22	0.036

ACE indicates angiotensin converting enzyme; ARB, angiotensin receptor blockers; HFmrEF, heart failure with midrange ejection fraction; HFpEF, heart failure with preserved ejection fraction; and HFrEF, heart failure with reduced ejection fraction.

during exercise, and RV fractional area at rest and at peak exercise were progressively reduced (Table 4).

Predictors of Peak VO$_2$ and VE/VCO$_2$ Slope

Univariate analysis showed a significant association between peak VO$_2$ and age (*R*=−0.50), E/e′ at rest (*R*=−0.44), peak CO (*R*=0.67), LVEF (*R*=0.39), peak mitral regurgitation ≥2 (*R*=−0.39), LA strain during exercise (*R*=−0.46), and mPAP/CO slope (*R*=−0.55) (Table 5). At the multivariable analysis, peak CO (β-coefficients=0.72) emerged as the strongest predictor of peak VO$_2$ along with age (β-coefficients=−0.108) and E/e′ at rest (β-coefficients=−0.66). The CO over exercise workload and mPAP/CO relationship for Weber (A and C) and VC (B and D) classes are reported in Figure 1.

As for VE/VCO$_2$ slope there were significant associations with age (*R*=0.22), male sex (*R*=0.15), E/e′ at rest (*R*=0.46), LVEF at rest (*R*=−0.40), peak CO (*R*=−0.44), peak mitral regurgitation ≥2 (*R*=0.38), LA strain during exercise (*R*=−0.46), and peak TAPSE/PASP ratio (*R*=−0.50). At multivariable analysis, mPAP/CO slope (β-coefficients=0.39) emerged as the strongest predictor of VE/VCO$_2$ slope along with E/e′ at rest (β-coefficients=−0.13) and peak mitral regurgitation >2 (β-coefficients=2.38).

Outcome Analysis

During the follow-up (median, 761 days; interquartile range, 364–1201 days; n=195), 45 patients with HFrEF (n=28), HF with midrange ejection fraction (n=9), and HFpEF (n=8) had the composite end point of hospitalization for HF/mortality (*P*=0.05 for events among HF subgroups according to LVEF). Cox proportional hazard regression analyses showed that Weber (hazard ratio [HR], 2.9; 95% CI, 1.8–4.7; *P*<0.001) and VC classes (HR, 1.4; 95% CI, 1.1–2.0; *P*=0.017) were independently associated with the composite end point after adjustment for age and sex (Table 6). Kaplan–Meier survival curves for Weber (log-rank *P*<0.001) and VC classes (log-rank *P*=0.049) are reported in Figure 2A and 2B, respectively.

The receiver operating characteristic curves demonstrated peak CO >4 L/min to be the optimal cutoff point for the composite end point with the area under the receiver operating characteristic curve (area under the curve, 0.63; 95% CI, 0.53–0.73; Figure 3A).

Table 4. CPET and Exercise Echocardiographic Variable in 4 Groups According to Ventilatory Classes

	Ventilatory Class 1 (n=143)	Ventilatory Class 2 (n=73)	Ventilatory Class 3 (n=35)	Ventilatory Class 4 (n=18)	*P* Value
Peak VO_2, mL/kg per min	16.9±6.2	13.5±3.8	12.4±3.7	10.3±2.7	<0.001
Percent predicted peak VO_2, %	65±20	63±23	58±22	49±14	0.007
VE/VCO_2 slope	26.2±2.5	32.4±1.6	38.7±2.6	52.5±9.1	…
EOV, %	25	32	44	72	<0.001
$\Delta VO_2/\Delta WR$ flattening, %	11	21	17	33	0.071
LV mass index at rest, g/m^2	108±30	130±38	147±46	149±34	<0.001
LV end-diastolic volume index at rest, mL/m^2	65±25	77±30	94±49	108±26	<0.001
E/e′ at rest	12.4±6.7	18.3±11.4	23.8±12.8	26.9±10.1	<0.001
LV ejection fraction at rest, %	50±16	40±14	37±13	30±11	<0.001
Peak LV cardiac output, L/min	7.8±2.4	6.0±2.0	5.3±1.8	4.8±1.6	<0.001
Peak cardiac power output, mm Hg/L per min	1.98±0.71	1.42±0.56	1.21±0.50	1.03±0.41	<0.001
Mitral regurgitation ≥2 at rest, %	13	37	57	78	<0.001
Peak mitral regurgitation ≥2, %	25	56	60	89	<0.001
Left atrial volume index at rest, mL/m^2	32.6±14.3	42.3±22.1	55.2±26.0	64.8±24.4	<0.001
Left atrial stiffness at rest	0.39 (0.21–0.64)	0.89 (0.37–1.66)	1.61 (0.76–3.30)	2.69 (1.53–3.39)	<0.001
Abnormal left atrial stiffness, %	28	68	88	100	<0.001
Left atrial strain at rest, %	29.4±12.4	20.9±11.9	15.4±9.8	10.5±4.9	<0.001
Left atrial strain during exercise, %	31.3±14.7	18.8±11.1	16.6±10.7	10.8±6.1	<0.001
Mean PAP/cardiac output slope, mm Hg/L per min	3.1 (2.2–4.7)	5.3 (2.6–8.0)	6.1 (3.4–10.5)	7.6 (4.2–18.2)	<0.001
Systolic PAP at rest, mm Hg	29±8	32±9	39±21	51±19	<0.001
Peak systolic PAP, mm Hg	48±12	52±12	60±16	64±13	<0.001
TAPSE at rest, mm	21.0±4.0	18.1±5.0	17.1±4.4	14.6±3.8	<0.001
Peak TAPSE, mm	24.4±4.8	19.8±5.5	18.2±4.6	16.3±4.3	<0.001
TAPSE/systolic PAP at rest, mm/mm Hg	0.79±0.26	0.62±0.26	0.51±0.25	0.34±0.15	<0.001
Peak TAPSE/systolic PAP, mm/mm Hg	0.55±0.23	0.41±0.18	0.31±0.10	0.26±0.10	<0.001
RV fractional area change at rest, %	49±9	43±12	39±12	33±11	<0.001
Peak RV fractional area change, %	49±10	40±15	35±13	31±5	<0.001

CPET indicates cardiopulmonary exercise test; E/e′, the ratio of the mitral peak velocity of the early filling (E) wave to early diastolic mitral annular velocity (e′); EOV, exercise oscillatory ventilation; LV, left ventricular; PAP, pulmonary artery pressure; RV, right ventricular; TAPSE, tricuspid annual plane systolic excursion; VE/VCO_2, ventilation over CO_2; and $\Delta VO_2/\Delta WR$, Δ oxygen consumption/Δ work rate.

After adjusting for age and sex, a peak CO <4 L/min was also associated with poor outcome (HR, 3.7; 95% CI, 2.0–6.8; $P<0.001$; Table 6). Kaplan–Meier survival curves of peak CO are reported in Figure 3B. The receiver operating characteristic curves for mPAP/CO slope identified the best cutoff as 4.2 mm Hg/L per minute (area under the curve, 0.63; 95% CI, 0.52–0.73; Figure 3C). After adjusting for age and sex, an mPAP/CO slope cutoff of 4.2 mm Hg/L per minute was also associated with poor outcome (HR, 1.8; 95% CI, 0.97–3.5; $P=0.06$). Kaplan–Meier survival curves of mPAP/CO are reported in Figure 3D.

Combined Weber and VC Classes Analyses

Figure 4A shows the inverse exponential relationship of VE/VCO_2 slope versus peak VO_2 according to the Weber and VC subdivisions. The best prognostic stratification was observed when combining to Weber (A/B or C/D) and severe ventilation inefficiency (VC-4 or not) differentiating between low and high clinical risk (Figure 4B, log-rank $P<0.001$). At Cox proportional hazard regression analyses, the combined stratification of Weber and ventilatory class was independently associated with the composite end point, after adjustment for age and sex (HR, 2.7; 95% CI, 1.6–4.8; $P<0.001$); age, sex, and E/e′ at rest (HR, 1.8; 95% CI, 1.2–2.8; $P=0.009$); age, sex, and peak mitral regurgitation ≥2 (HR, 2.1, 95% CI, 1.1–4.2; $P=0.007$); and age, sex, and mPAP/CO slope (HR, 1.6, 95% CI, 1.02–2.6; $P=0.043$), but not after adjustment for age, sex, and peak CO (HR, 1.6; 95% CI, 0.97–2.6; $P=0.064$). Because of the high *R* value ($R=0.67$) between peak VO_2 and peak CO, statistical significance might be blunted after adjustment for peak CO. The combination between Weber classes C/D and VC-4

Table 5. Univariate and Multivariable Analysis for Peak VO_2 and VE/VCO_2 Slope

Variable	Univariate		Multivariable	
	R	*P* Value	β-Coefficients±SE	*P* Value
Peak VO_2, mL/kg per min				
Age, per y	−0.50	<0.001	−0.108±0.022	<0.001
Male sex (= 1)	0.10	0.105	…	…
E/e′ at rest	−0.44	<0.001	−0.06±0.03	0.032
LV ejection fraction at rest, %	0.39	<0.001	…	…
Peak LV cardiac output, L/min	0.67	<0.001	0.72±0.16	<0.001
Peak mitral regurgitation ≥2 (=1)	−0.39	<0.001	…	…
Left atrial strain during exercise, %	0.46	<0.001	…	…
Mean PAP/cardiac output slope, mm Hg/L per min	−0.33	<0.001	…	…
VE/VCO_2 slope				
Age, per y	0.24	<0.001	…	…
Male sex (=1)	0.15	0.018	2.44±1.01	0.017
E/e′ at rest	0.46	<0.001	0.13±0.05	0.009
LV ejection fraction at rest, %	−0.40	<0.001	…	…
Peak LV cardiac output, L/min	−0.44	<0.001	…	…
Peak mitral regurgitation ≥2 (=1)	0.38	<0.001	2.38±1.05	0.024
Left atrial strain during exercise, %	−0.46	<0.001	…	…
Mean PAP/cardiac output slope, mm Hg/L per min	0.55	<0.001	0.39±0.06	<0.001

E/e′ indicates the ratio of the mitral peak velocity of the early filling (E) wave to early diastolic mitral annular velocity (e′); LV, left ventricular; PAP, pulmonary artery pressure; and TAPSE, tricuspid annual plane systolic excursion.

exhibited the worst gas exchange phenotype. The main and significant hemodynamic differences were observed in terms of peak CO, LA strain during exercise, and peak mPAP/CO slope (Figure 5). No significant interaction was found between the combined Weber and VC stratification with $\Delta VO_2/\Delta WR$ flattening (*P*=0.22) and peak mitral regurgitation (*P*=0.8). An interaction between the combined stratification and EOV (*P*=0.09) was observed at Cox proportional hazard regression analyses. Interestingly, at sensitive analysis, the combined class stratification differentiated between patients with low and high clinical risk according to peak mitral regurgitation severity <2 (log-rank *P*=0.01, n=119; and ≥2 log-rank *P*=0.045, n=76).

DISCUSSION

Despite recent advancements in HF treatment, the prognosis still needs to be improved, and it is important that we continue to refine our ability to accurately identify patients with HF at the highest risk for morbidity and mortality, referring these patients earlier for advanced therapeutic strategies.[25]

We aimed at revisiting and refining the clinical applicability and prognostic information of the Weber and VC classifications by combining gas exchange analysis with hemodynamic assessment by CPET imaging. The main study findings are as follows: (1) in a contemporary population of patients with HF incorporating the entire spectrum of LVEF phenotypes, the Weber and VC classes maintained the ability to predict outcome after adjustment for age and sex; (2) the best risk prediction model was observed when the 2 classifications were used in combination and analyzing data by regression models controlling for confounders; (3) a limited CO at peak exercise (cutoff of 4 mL/min per kg) and an impaired RV to pulmonary circulation coupling (mPAP versus CO relationship; cutoff of 4.2) were the best hemodynamic determinants of peak VO_2 and VE/VCO_2 slope, respectively.

Implications of the Weber and VC Classifications in a Contemporary HF Cohort

Historically, the Weber[3] and VC[9] classifications have guided clinicians through the objective quantification of exercise impairment and symptoms definition. These classifications have provided reference cutoffs for the 2 most important CPET predictive variables, that is, peak VO_2 and VE/VCO_2 slope to be used in HFrEF for risk prediction and proper timeline for advanced treatments, such as heart transplantation.[5,26] Over time,

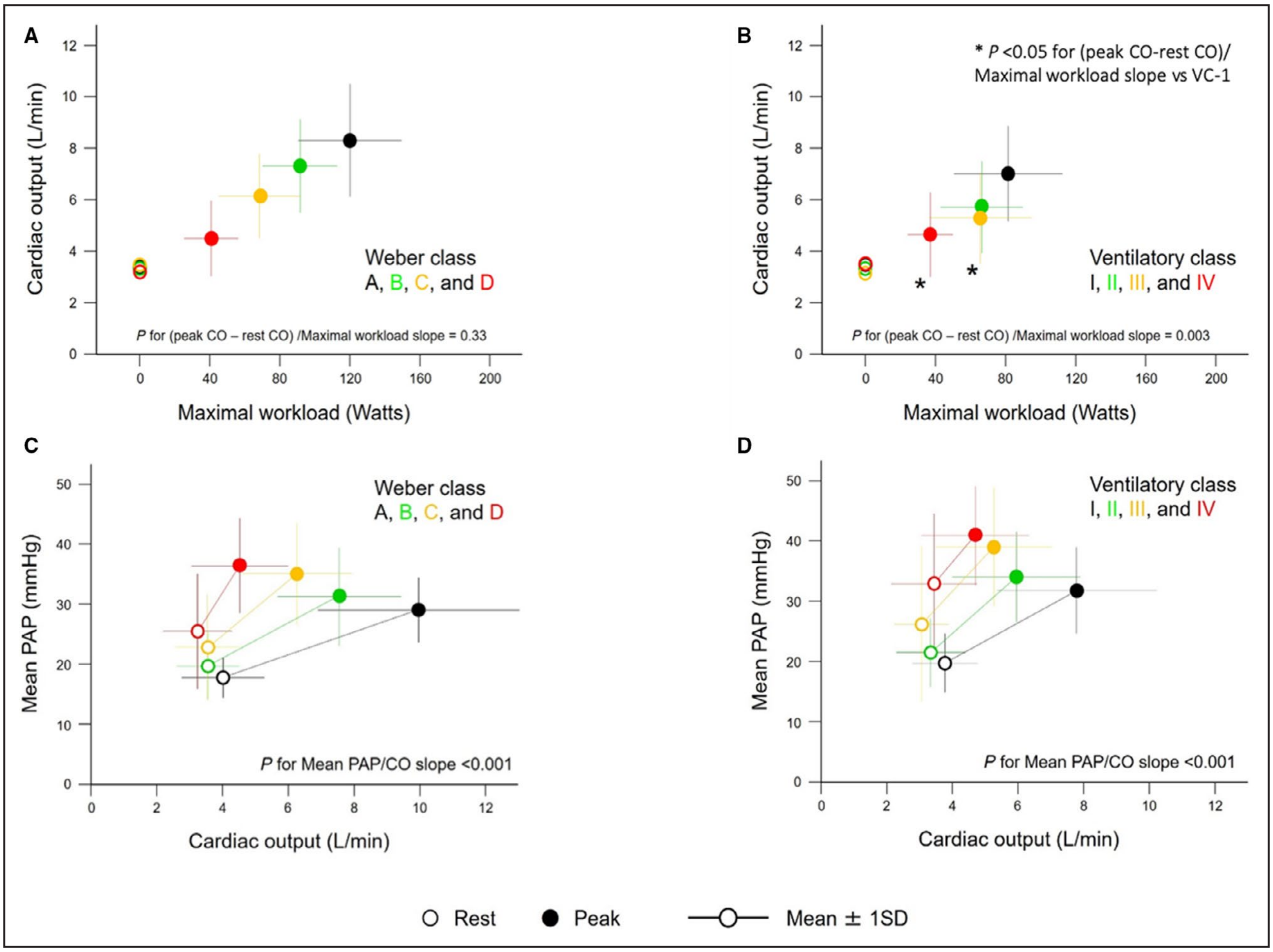


Figure 1. Linear relationship between rest to peak CO and maximal work rate for Weber (A) and VC (B) classes Kaplan-Meier and mPAP/CO slope changes rest to peak for weber (C) and VC classes (D).
CO indicates cardiac output; mPAP, mean pulmonary artery; and VC, ventilatory class.

dichotomic cutoffs have been proposed, which have been changed with the progressive introduction of therapies and interventions significantly impacting the natural course of the disease. One of the most striking examples has been the "revision" of prognostic cutoffs for peak VO_2, once beta-blockers have become an integrative part of HF treatment.[27,28]

A recent analysis involving a large cohort of patients with HF showed a reduction in the mortality rate associated with specific cutoff values for peak VO_2 and VE/VCO_2 slope, which were derived according to a dichotomic approach. They reported how the previously validated predictive cutoff for VO_2 and VE/VCO_2 slope have changed over the past 20 years.[10]

Although this information can be taken as a guidance through a better refinement of clinical decision making, they do not clarify how the Weber and VC classifications apply to the contemporary HF phenotypes and questions the potential implications derived from using these categorization approaches. Of note, results were limited to a population of exclusively patients with HFrEF lacking the full spectrum of HF, especially HF with midrange ejection fraction and HFpEF,[29] without performing data analysis in a continuous model and using regression models for confounders.

Our findings fully support the role of the Weber and VC multilevel classifications demonstrating an unaltered prognostic significance of either classification in a modern cohort of HF. The best predictive model was, however, obtained by combining Weber classes with VC classes, and our findings support their integrated use with the Weber classes A/B and VC-1, which seem useless when assessed alone.

The value of risk stratification by combining peak VO_2 and VE/VCO_2 slope has been proposed in the past[30,31] without defining the underlying hemodynamic patterns, the predominant determinants, and their association with gas exchange variables.

Considering the limited evidence on CPET prognostic scores and multilevel classificatory systems in HFpEF[31–35] and HF with midrange ejection fraction,[17,32,33] our observations provide new perspectives on the use

Table 6. Age and Sex Adjusted Hazard Ratio for HF Hospitalization/Mortality

	Adjusted Hazard Ratio	95% CI
Weber class	2.9	1.8–4.7
A=1		
B=2		
C=3		
D=4		
Ventilatory class	1.4	1.1–2.0
Peak cardiac output, <4 L/min=1	3.7	2.0–6.8
Mean PAP/cardiac output slope, ≥4.2 mm Hg/L per min=1	1.8	0.97–3.5
The combined stratification using Weber and ventilatory classes	2.1	1.3–3.5
Weber class A/B=1		
Weber classes C/D without ventilatory class 4=2		
Weber classes C/D with ventilatory class 4=3		

HF indicates heart failure; and PAP, pulmonary artery pressure.

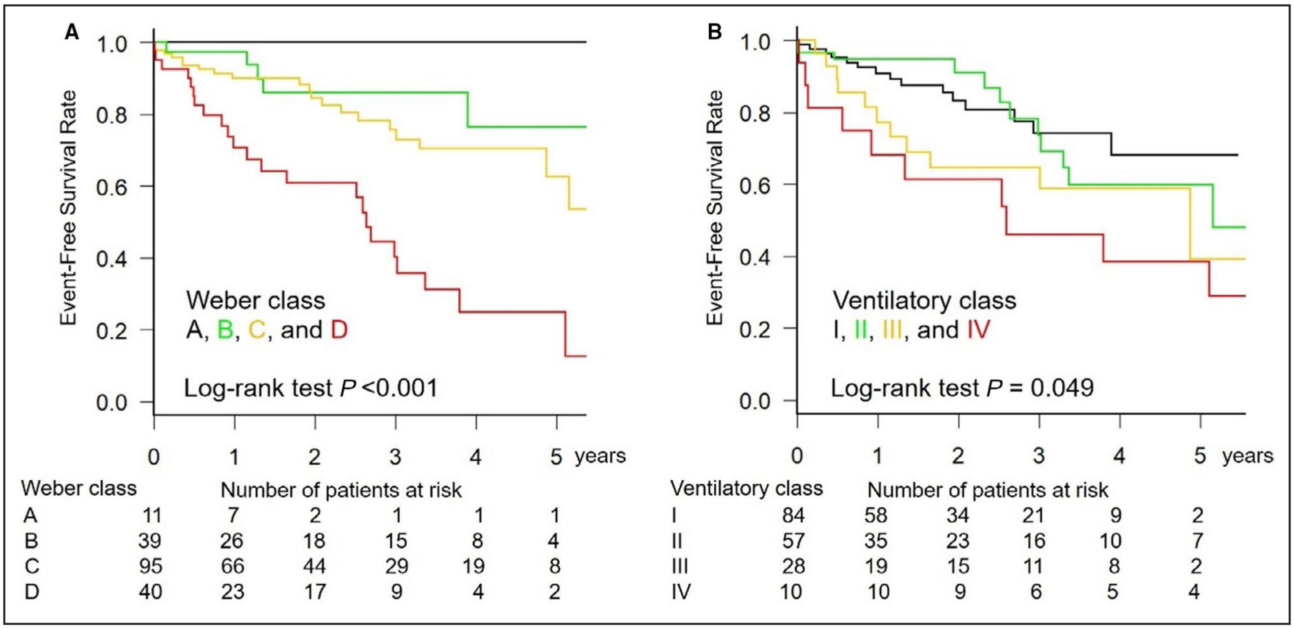
of gas analysis classificatory systems in the continuum of LVEF phenotypes, overcoming, in some instances, the need of using LVEF categorization for HF syndrome.

Added Value of CPET Imaging to the Weber and VC Classifications

When Weber and coworkers introduced their classificatory system, a firm link was reported between invasively measured cardiac index changes during exercise and O_2 uptake, showing that the limited CO increase and O_2 supply rather than peripheral O_2 extraction is the key limiting step to exercise performance in HF.[34,35] In agreement, we report the same ability to define exercise impairment by noninvasively measured CO by echo-Doppler technique with a linear stepwise reduction according to increasing classes. Interestingly, at multivariable analysis, CO at peak exercise emerged as the most powerful hemodynamic determinant of peak VO_2, with a cutoff of 4 L/min at peak exercise identified as the best discriminator of outcome in the entire population.

When Arena and coworkers proposed the VC classificatory system, the hemodynamic assessment was not part of their algorithm. Studies investigating hemodynamic correlates and determinants of VE/VCO_2 slope have consistently shown that the highest ventilatory slope correlates are the coexistence of RV dysfunction and the increased pulmonary pressure and pulmonary vascular resistances.[8,31,36] An elevated mPAP/CO slope during exercise, an endurance indicator of RV to pulmonary circulation coupling, emerged as the most powerful variable related to an impaired ventilation efficiency and a VE class-dependent upward shift in the mPAP/CO slope was observed. Our findings extended even to patients with HFpEF, through the noninvasive approach, to the landmark observations recently reported by Nayor et al.[37]

Out of the specific hemodynamic determinants, findings point to the multifold putative mechanisms involved in CO limitation. Interestingly, the impairment in the LA dynamics, in the LV filling and the degree of mitral



Number of patients at risk

Weber class	0	1	2	3	4	5
A	11	7	2	1	1	1
B	39	26	18	15	8	4
C	95	66	44	29	19	8
D	40	23	17	9	4	2

Ventilatory class	0	1	2	3	4	5
I	84	58	34	21	9	2
II	57	35	23	16	10	7
III	28	19	15	11	8	2
IV	10	10	9	6	5	4

Figure 2. Kaplan-Meier stratification according to Weber (A) and VC (B) classifications.
VC indicates ventilator class.

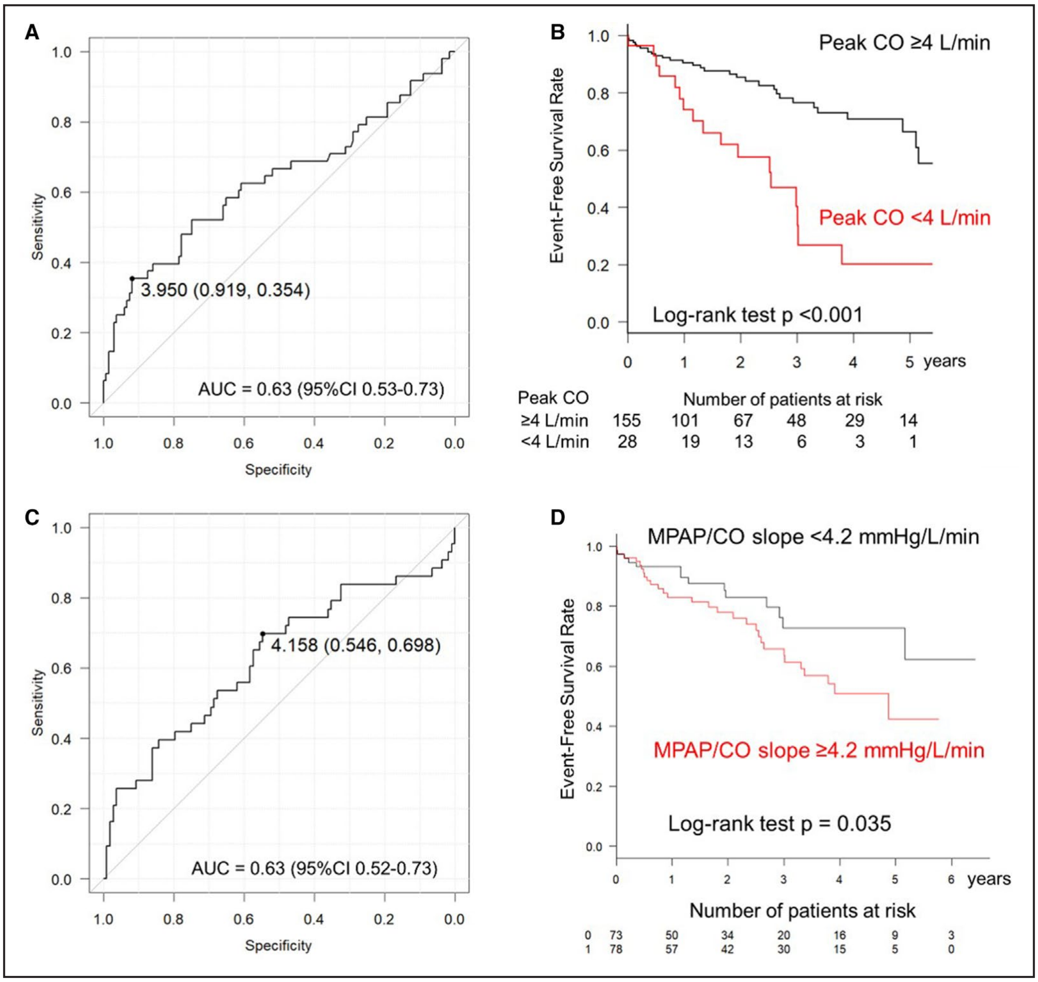


Figure 3. ROC curve analysis for the best CO slope and mPAP/CO slope (A and C) and Kaplan-Meir analyses using the best identified cutoff for peak CO (≥4 L/min, B) and mPAP/CO slope (≥4.2 mm Hg/L per min, D).

CO indicates cardiac output; and MPAP, mean pulmonary pressure.

regurgitation were progressively impaired throughout Weber and VC classes, further stressing the concept that the blunted cardiac reserve is the main driver of gas exchange abnormalities encountered in HF.

Overall, these findings support the idea that CPET imaging can be a reliable alternative to the invasively obtained measures during maximal performance, filling the gap between isolated gas exchange assessment and the key limiting steps in the hemodynamic response. This approach may clearly facilitate and remarkably improve accuracy in the daily ambulatory practice.

Study Limitations

The cutoff of a CO of 4 L/min as well as of an mPAP/CO_2 slope of 4.2 mm Hg/L per minute emerged as best predictors of worse Weber and VC classifications need, of course, to be confirmed in different laboratories. Twenty-five percent of patients with HFrEF were receiving sacubitril/valsartan therapy, a rate too low for specifically addressing a subgroup analysis on this population. It appears, however, that the classifications maintain specific and straightforward prognostic ability for the most advanced classes, and future studies should further confirm or deny how much staging the Weber A/B and VC-1/2 classes can still provide an optimal stratification of risk in optimally treated patients. Of note, in recent years because of the rapid advancement in evidence base and availability of many therapeutic options and decision-making algorithms, CPET imaging would not be the main reference test in the final indication to heart transplantation as CPET classifications, especially the Webe classification, have been in the past.

Overall, our findings may be of potential limited generalizability to the entire spectrum of patients with HF

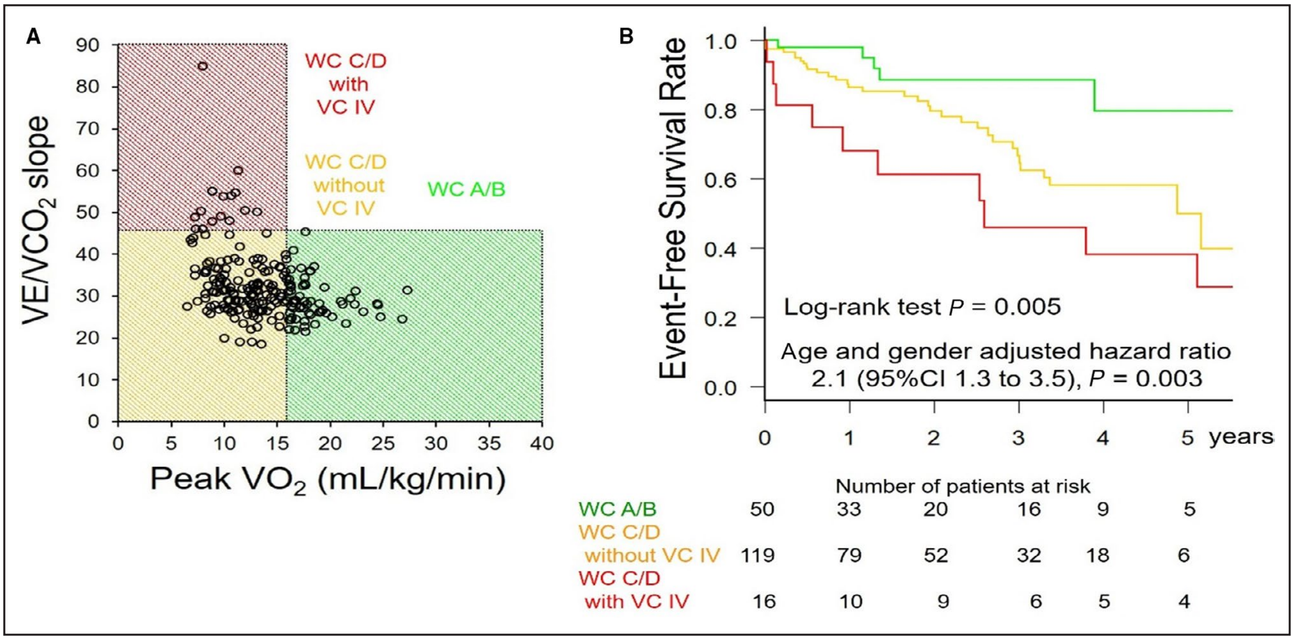


Figure 4. Distribution of VE/VCO$_2$ slope vs peak VO$_2$ according to VC C/D with and without VC IV (A).
Kaplan-Meier survival analysis of Weber classification and VC combinations (**B**). VC, indicates ventilatory classification; VE/VCO$_2$, ventilation to carbon dioxide production; VO$_2$, oxygen consumption and WC, Weber classification.

because of the lack of representation of patients on pacing and with poor echocardiography quality.

CONCLUSIONS AND PERSPECTIVES

Revisiting and phenotyping the Weber and VC classification by CPET imaging in a contemporary HF population has yielded to some noteworthy implications. Both classifications still appear valuable and updated for HF populations throughout the LVEF subdivision, supporting the European Society of Cardiology Guidelines HF classificatory system. The best risk prediction model was observed when the 2 classificatory systems were combined.

CO and mPAP/CO slope emerged as the best determinants of peak VO$_2$ and VE/VCO$_2$ slope, respectively. Hemodynamic variables emerged as strongly predictive of worse outcome, and may well represent the hemodynamic determinants to be addressed and targeted in daily ambulatory practice to improve exercise performance, symptoms, and, very likely, prognosis across the wide spectrum of the HF population.

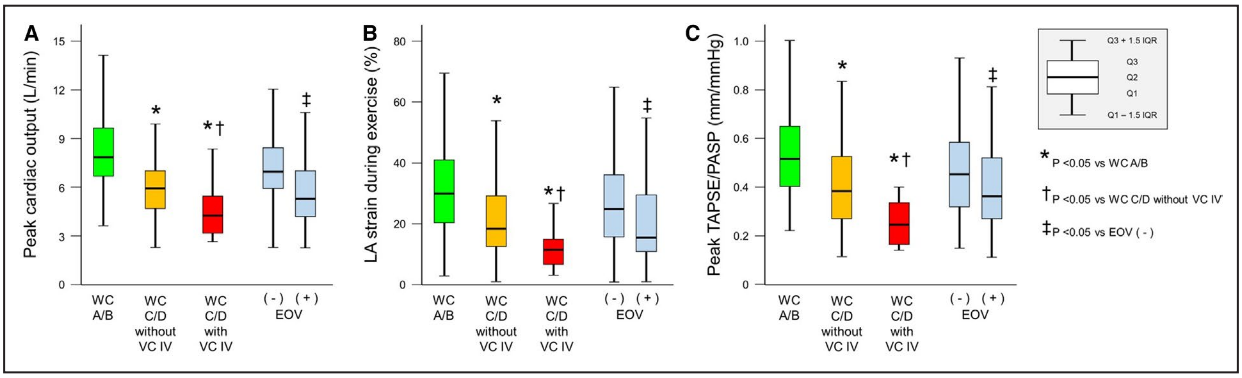


Figure 5. Peak CO (A), left atrial strain (B) and mPAP/CO slope (C) among the 3 groups according to the Weber and ventilatory classifications and in patients with and without EOV.
T-test or Mann-Whitney *U* test were used to compare differences between patients with and without EOV. EOV indicates exercise oscillatory ventilation; VC, ventilatory classification; and WC, Weber classification.

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Disclosures

None.

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