ORIGINAL RESEARCH

Prognostic Value of Cardiopulmonary Exercise Testing in Heart Failure With Reduced, Midrange, and Preserved Ejection Fraction

Wilson Nadruz, Jr, MD, PhD; Erin West, MSc; Morten Sengeløv, MB; Mário Santos, MD; John D. Groarke, MBBCh, MPH; Daniel E. Forman, MD; Brian Claggett, PhD; Hicham Skali, MD, MSc; Amil M. Shah, MD, MPH

***Background*—**This study aimed to compare the independent and incremental prognostic value of peak oxygen consumption (VO_2) and minute ventilation/carbon dioxide production (VE/VCO_2) in heart failure (HF) with preserved (HFpEF), midrange (HFmEF), and reduced (HFrEF) ejection fraction (LVEF).

***Methods and Results*—**In 195 HFpEF (LVEF ≥50%), 144 HFmEF (LVEF 40–49%), and 630 HFrEF (LVEF <40%) patients, we assessed the association of cardiopulmonary exercise testing variables with the composite outcome of death, left ventricular assist device implantation, or heart transplantation (256 events; median follow-up of 4.2 years), and 2-year incident HF hospitalization (244 events). In multivariable Cox regression analysis, greater association with outcomes in HFpEF than HFrEF were noted with peak VO_2 (HR [95% confidence interval]: 0.76 [0.67–0.87] versus 0.87 [0.83–0.90] for the composite outcome, $P_{interaction}$=0.052; 0.77 [0.69–0.86] versus 0.92 [0.88–0.95], respectively for HF hospitalization, $P_{interaction}$=0.003) and VE/VCO_2 slope (1.11 [1.06–1.17] versus 1.04 [1.03–1.06], respectively for the composite outcome, $P_{interaction}$=0.012; 1.10 [1.05–1.15] versus 1.04 [1.03–1.06], respectively for HF hospitalization, $P_{interaction}$=0.019). In HFmEF, peak VO_2 and VE/VCO_2 slope were associated with the composite outcome (0.79 [0.70–0.90] and 1.12 [1.05–1.19], respectively), while only peak VO_2 was related to HF hospitalization (0.81 [0.72–0.92]). In HFpEF and HFrEF, peak VO_2 and VE/VCO_2 slope provided incremental prognostic value beyond clinical variables based on the C-statistic, net reclassification improvement, and integrated diagnostic improvement, with models containing both measures demonstrating the greatest incremental value.

***Conclusions*—**Both peak VO_2 and VE/VCO_2 slope provided incremental value beyond clinical characteristics and LVEF for predicting outcomes in HFpEF. Cardiopulmonary exercise testing variables provided greater risk discrimination in HFpEF than HFrEF. **(*J Am Heart Assoc*.2017;6:e006000. DOI: 10.1161/JAHA.117.006000.)**

Key Words: cardiopulmonary exercise testing • ejection fraction • heart failure • oxygen consumption • preserved ejection fraction

Cardiopulmonary exercise testing (CPET) is routinely used in the prognostic evaluation of patients with heart failure (HF) with reduced ejection fraction (HFrEF), in whom the prognostic value of peak oxygen consumption (VO_2) and the minute ventilation/carbon dioxide production (VE/VCO_2) slope is powerful and well established.[1,2] However, it is well recognized that HF may occur with any ejection fraction (left ventricular ejection fraction [LVEF]). Indeed, HF with preserved ejection fraction (HFpEF) accounts for greater than half of HF cases, and is associated with a heightened risk of HF hospitalization and death similar to HFrEF.[3–5] Pathophysiologic heterogeneity has frustrated efforts to develop efficacious interventions in HFpEF, highlighting the need for better approaches to identify relevant physiologic and prognostic subgroups.[6,7] Variability in the LVEF cutoff used for the definition of HFpEF contributes to this heterogeneity. Recent

From the Division of Cardiovascular Medicine, Brigham and Women's Hospital, Boston, MA (W.N., E.W., M. Sengeløv, J.D.G., B.C., H.S., A.M.S.); Department of Internal Medicine, University of Campinas, Brazil (W.N.); Faculty of Medicine of University of Porto, Portugal (M. Santos); Department of Cardiology, University of Pittsburgh Medical Center, Pittsburgh, PA (D.E.F.); VA Pittsburgh Healthcare System, Pittsburgh, PA (D.E.F.).

Accompanying Tables S1 through S5 and Figure S1 are available at http://jaha.ahajournals.org/content/6/11/e006000/DC1/embed/inline-supplementary-material-1.pdf

Correspondence to: Amil M. Shah, MD, MPH, Division of Cardiovascular Medicine, Brigham and Women's Hospital, 75 Francis St, Boston, MA 02445. E-mail: ashah11@partners.org

Received March 1, 2017; accepted August 7, 2017.

Clinical Perspective

What Is New?

- Peak oxygen consumption is robustly predictive of worse prognosis in heart failure with preserved ejection fraction, heart failure with midrange ejection fraction, and heart failure with reduced ejection fraction.
- Among patients with heart failure with preserved ejection fraction, both peak oxygen consumption and minute ventilation/carbon dioxide production slope provided incremental prognostic value beyond relevant clinical covariates for long-term adverse outcomes.
- Cardiopulmonary exercise testing variables provided greater risk discrimination in heart failure with preserved ejection fraction compared with heart failure with reduced ejection fraction.

What Are the Clinical Implications?

- These findings support the notion that cardiopulmonary exercise testing is a robust albeit underutilized tool for risk stratification in heart failure with preserved ejection fraction.
- Further studies may be necessary to assess whether peak oxygen consumption and minute ventilation/carbon dioxide production slope are measures that should be systematically incorporated into decision algorithms for clinicians aiming to stratify risk and prognosis in heart failure patients across the left ventricular ejection fraction spectrum.

guidelines therefore introduced a novel classification schema for HF based on LVEF, adding HF with midrange LVEF (HFmEF; LVEF 40–49%) to HFpEF (≥50%) and HFrEF (LVEF <40%), with the expressed aim of fostering greater research into characteristics and pathophysiology of this understudied group.[8]

Exercise intolerance is a cardinal symptom of HF regardless of LVEF.[9] Objective assessment of functional capacity by CPET has been increasingly used both as a diagnostic tool[10] and as a surrogate efficacy end point in HFpEF therapeutic clinical trials.[11,12] However, the few studies that have assessed the relationship between peak VO_2 and VE/VCO_2 slope and prognosis in HFpEF have produced conflicting results, and none have evaluated their relevance for HF hospitalization—an important source of morbidity in HFpEF.[13–16] Furthermore, the prognostic value of CPET testing in HFmEF specifically has not been described. To evaluate the utility of CPET as a widely available diagnostic and prognostic tool in HFpEF and HFmEF, the present study aimed to define and compare the independent and incremental prognostic value of peak VO_2 and VE/VCO_2 slope for HF hospitalization and the composite of death, left ventricular assist device (LVAD) implantation or heart transplant in HFpEF, HFmEF, and HFrEF patients.

Methods

Study Population

This study included 973 HF patients who underwent clinically indicated CPET at the Brigham and Women's Hospital between July 2007 and December 2012 as previously described.[17] Participants with missing baseline LVEF data (n=4) were excluded, resulting in 969 subjects for the analysis. The study was approved by the Partners Human Research Committee, which waived the requirement for informed consent.

Classification of HF Patients

LVEF was assessed at the Brigham and Women's Hospital by quantitative echocardiography. Values of LVEF were obtained from echocardiography examinations that were most contemporary to the CPET dates (median time difference [25th, 75th percentiles]=0 [0, 10] days). For the primary analysis, participants were categorized based on LVEF as HFrEF if the LVEF was <40% (n=630), HFmEF if the LVEF was 40% to 49% (n=144), and HFpEF if the LVEF was ≥50% (n=195), as suggested by current guidelines.[8]

Clinical Variables Definition

Information regarding patients' demographics, body mass index, blood pressure, heart rate, current medications, presence of implantable cardioverter-defibrillator, cardiac resynchronization therapy, or pacemaker, and gas-exchange variables were collected at the time of CPET. Further clinical characteristics (comorbidities and New York Heart Association Classification) and laboratory values (hemoglobin and creatinine) most contemporary to CPET dates were obtained from chart review. Antiarrhythmic medications included digoxin and amiodarone. The Chronic Kidney Disease Epidemiology Collaboration formula was used to estimate glomerular filtration rate.[18] Chronic kidney disease was defined as estimated glomerular filtration rate <60 mL/min per 1.73 m^2. Anemia was defined as hemoglobin <12 g/dL in women and <13 g/dL in men. Angiotensin-converting-enzyme inhibitors and angiotensin receptor blockers were coded into a single variable, while cardiac resynchronization therapy and implantable cardioverter-defibrillator were coded as a single variable.

Exercise Protocol

Exercise tests were performed in the Brigham and Women's Hospital cardiopulmonary exercise laboratory with the subjects breathing room-air, using ramp protocols.[17] Symptom-

limited CPET was performed on all subjects. Pharmacological therapy was continued before and through exercise testing. The equipment was calibrated daily as recommended by the manufacturer. VO_2, carbon dioxide production (VCO_2), and minute ventilation (VE) were acquired breath-by-breath and averaged over a 10-second interval, using a ventilatory expired gas analysis system (MGC Diagnostics, St. Paul, MN). Peak VO_2 was defined as the highest 10-second averaged VO_2 during the last stage of the symptom-limited exercise test. The Wasserman formula was used to determine percent of predicted peak VO_2.[19] VE/VCO_2 slope was calculated from rest to the gas exchange at peak exercise. Blood pressure was measured using a standard cuff sphygmomanometer. Resting and peak heart rate were obtained from the associated-CPET ECGs. Age-predicted maximal heart rate was estimated by Astrand's formula[20]: 220—age (years). Chronotropic index was calculated as: (peak heart rate−resting heart rate)/(age-predicted maximal heart rate−resting heart rate).[21]

Outcomes

Clinical outcomes included the composite outcome of all-cause death, LVAD implantation, or heart transplantation up to December 31, 2014, and incident and total HF hospitalization up to 2 years post-CPET. LVAD implantations, heart transplantations, and HF hospitalizations were abstracted by chart review by individuals who were blinded to CPET data. HF hospitalizations were defined as any hospitalization for treatment or management of HF. All-cause death was determined using the National Death Index.

Statistical Analysis

Continuous variables are expressed as mean±SD for normally distributed data or median [25th, 75th percentiles] for non-normally distributed data. Categorical variables are expressed as number of subjects and proportion. Comparisons of clinical and CPET features among the studied groups were performed using 1-way ANOVA for normally distributed variables, Kruskal–Wallis test for non-normally distributed variables, and χ^2 test for categorical variables. The rates of incident outcomes are expressed as events per 100 person-years at risk.

Univariate and multivariable Cox regression models were used to assess the unadjusted and adjusted association between unit decrease of peak VO_2 and unit increase of VE/VCO_2 slope and the studied outcomes within each LVEF category. For the composite outcome of death, LVAD, or transplant, models used follow-up through December 31, 2014 (median [interquartile range]=4.2 [2.8–5.6], 3.9 [2.5–5.5], 4.8 [3.2–5.8], and 4.5 [3.1–5.8] years for the total, HFrEF, HFmEF, and HFpEF samples, respectively). For incident HF hospitalization, models used follow-up through 2 years post-CPET (median [interquartile range]=2.0 [0.2–2.0], 1.6 [0.1–2.0], 2.0 [0.5–2.0], and 2.0 [1.2–2.0] years for the total, HFrEF, HFmEF, and HFpEF samples, respectively). The relationship between peak VO_2 and VE/VCO_2 slope and total HF hospitalization was evaluated using negative binomial models for recurrent events. For all Cox regression and negative binomial regression analyses, we used an overall model including LVEF as a categorical variable. However, we noted a violation of the proportionality assumption when including all patients in the same Cox regression model. We therefore used stratified Cox models using LVEF category as a stratification factor. Multivariable models adjusted for the following established prognostic variables in HF: age, sex, LVEF, chronic kidney disease, resting heart rate, resting systolic blood pressure, and coronary artery disease. The interaction between CPET variables and HF categories for the studied outcomes was assessed using interaction terms. The incremental value of peak VO_2 and VE/VCO_2 slope when added to clinical covariates either individually or together was evaluated using C-statistic, continuous net reclassification improvement (NRI), and integrated diagnostic improvement (IDI) with time-to-event data.[22] All C-statistics values were obtained via leave-1-out cross validation. The clinical covariates included age, sex, LVEF, chronic kidney disease, resting heart rate, resting systolic blood pressure, and coronary artery disease. In secondary analysis, we categorized the HFpEF, HFmEF, and HFrEF groups using cutoff points for CPET variables that are reported to be of prognostic significance (14 mL/min per kg for peak VO_2 and 30 for VE/VCO_2 slope),[1] and compared incidence rates of the studied outcomes between high and low peak VO_2 and VE/VCO_2 slope within each LVEF group. We also performed the following sensitivity analyses, which consisted of repeating the primary analysis after (1) considering the composite of incident HF hospitalization, death, transplant, or LVAD implantation at 2 years post-CPET as the outcome; and (2) substituting percent of peak VO_2 based on the Wasserman formula[19] for peak VO_2.

Statistical analysis was performed using Stata software Version 13.1 (Stata Corp LP, College Station, TX, USA). NRI and IDI analyses were performed using R software version 3.2.3. $P<0.05$ was considered significant.

Results

Clinical Characteristics

The mean age of the population was 55±14 years and was not significantly different between LVEF categories. While 33% overall were women, the prevalence was lowest in HFrEF and highest in HFpEF, with an intermediate prevalence in HFmEF.

HFrEF had a higher prevalence of diabetes mellitus and coronary artery disease, and lower prevalence of postchemotherapy status and New York Heart Association Class I, while HFmEF had lower prevalence of chronic kidney disease than the other LVEF groups (Table 1). Use of angiotensin-converting-enzyme inhibitors/angiotensin receptor blockers, β-blockers, aldosterone antagonists, diuretics, pacemakers, and cardiac resynchronization therapy/implantable cardioverter-defibrillator were all most common in HFrEF, while use of calcium channel blockers was most common in HFpEF. Use of these medical therapies tended to be intermediate in HFmEF when compared with HFrEF and HFpEF.

Cardiopulmonary Exercise Performance

HFpEF and HFmEF patients had a lower resting heart rate and higher resting systolic blood pressure than HFrEF patients.

Table 1. Baseline Clinical and Treatment Characteristics of Study Participants

Variables	HFrEF LVEF <50% (n=630)	HFmEF 40% to 49% (n=144)	HFpEF LVEF ≥50% (n=195)	*P* Value
Age, y	56±13	53±14	56±15	0.11
Male, n (%)	460 (73)	91 (63)	103 (53)	<0.001
White, n (%)	517 (82)	123 (85)	172 (88)	0.11
Body mass index, kg/m^2	28.3±5.7	29.0±6.5	29.4±7.0	0.06
NYHA, n (%)				<0.001
I	148 (23)	56 (39)	89 (46)	
II	219 (35)	56 (39)	59 (30)	
III	212 (34)	30 (21)	45 (23)	
IV	51 (8)	2 (1)	2 (1)	
Ischemic cardiomyopathy, n (%)	194 (31)	17 (12)	17 (9)	<0.001
Postchemotherapy, n (%)	38 (6)	20 (14)	21 (11)	0.003
Hypertension, n (%)	370 (59)	75 (52)	119 (61)	0.23
Diabetes mellitus, n (%)	185 (29)	28 (19)	37 (19)	0.003
Coronary artery disease, n (%)	262 (42)	37 (26)	43 (22)	<0.001
Atrial fibrillation, n (%)	223 (35)	42 (29)	55 (28)	0.10
COPD, n (%)	63 (10)	16 (11)	14 (7)	0.40
Chronic kidney disease, n (%)	193 (31)	24 (17)	47 (24)	0.002
Anemia, n (%)	158 (25)	35 (24)	58 (30)	0.38
LVEF, %	25 [19, 30]	42 [40, 45]	55 [50, 60]	
CRT/ICD, n (%)	344 (55)	38 (26)	25 (13)	<0.001
Pacemaker, n (%)	349 (55)	46 (32)	36 (18)	<0.001
β-Blocker, n (%)	565 (90)	123 (85)	134 (69)	<0.001
ACEI/ARB, n (%)	518 (82)	108 (75)	137 (70)	0.001
Aldosterone antagonist, n (%)	223 (35)	34 (24)	23 (12)	<0.001
Diuretic, n (%)	477 (76)	69 (48)	100 (51)	<0.001
Calcium channel blocker, n (%)	24 (4)	17 (12)	34 (17)	<0.001
Anticoagulation, n (%)	249 (40)	40 (28)	45 (23)	<0.001
Antiplatelet, n (%)	357 (57)	60 (42)	79 (41)	<0.001
Antiarrhythmic, n (%)	259 (41)	31 (22)	20 (10)	<0.001
Statin, n (%)	328 (52)	63 (44)	78 (40)	0.006

Data are presented as mean±SD for normally distributed variables and median [25th, 75th percentile] for non-normally distributed continuous variables. ACEI/ARB indicates angiotensin-converting-enzyme inhibitor or angiotensin receptor blocker; COPD, chronic pulmonary obstructive disease; CRT/ICD, cardiac resynchronization therapy and/or implantable cardioverter defibrillator; HFmEF, heart failure with midrange LVEF; HFpEF, heart failure with preserved LVEF; HFrEF, HF with reduced LVEF; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association Classification.

Table 2. Baseline Cardiopulmonary Exercise Testing Characteristics of Study Participants

Variables	HFrEF LVEF <50% (n=630)	HFmEF 40% to 49% (n=144)	HFpEF LVEF ≥50% (n=195)	*P* Value
Peak VO_2, mL/min per kg	14.3±5.2	17.1±7.1	17.4±7.8	<0.001
% predicted peak VO_2	56.5±18.2	66.6±19.3	72.9±21.2	<0.001
VE/VCO_2 slope	34.5±9.2	29.5±6.3	30.3±6.7	<0.001
Hemodynamic				
Resting heart rate, bpm	74±15	71±14	68±12	<0.001
Peak heart rate, bpm	121±28	128±29	127±28	0.005
Chronotropic index	0.51±0.29	0.59±0.27	0.60±0.26	<0.001
Resting SBP, mm Hg	114±19	120±20	123±20	<0.001
Peak SBP, mm Hg	135±27	150±27	154±31	<0.001
Resting DBP, mm Hg	73±11	75±12	74±11	0.14
Peak DBP, mm Hg	74±12	78±12	76±12	0.007
Peak RER	1.19±0.13	1.21±0.13	1.19±0.12	0.51

Data are presented as mean±SD. bpm indicates beats per minute; DBP, diastolic blood pressure; HFmEF, heart failure with midrange LVEF; HFpEF, heart failure with preserved LVEF; HFrEF, heart failure with reduced LVEF; LVEF, left ventricular ejection fraction; RER, respiratory exchange ratio; SBP, systolic blood pressure; VE/VCO_2, minute ventilation–carbon dioxide production relationship; VO_2, oxygen consumption.

Mean peak respiratory exchange ratio, a measure of exercise effort, was similar in all LVEF categories. With exercise, HFpEF and HFmEF patients showed higher peak heart rate, chronotropic index, and systolic and diastolic blood pressures than HFrEF patients. HFpEF and HFmEF participants had higher absolute and percent of predicted peak VO_2, and lower VE/VCO_2 slope compared with HFrEF participants (Table 2).

Outcomes

During a median follow-up of 4.2 [2.8–5.6] years, 256 patients (26% of the study sample) experienced the composite outcome (164 all-cause deaths, 37 LVAD implantations, and 55 heart transplantations). Annualized event rates were similar between the HFmEF and HFpEF groups, and considerably higher in the HFrEF group (Table 3). In multivariable Cox models containing clinical predictors, peak VO_2, and VE/VCO_2 slope, both peak VO_2 and VE/VCO_2 slope were independently associated with the composite outcome in HFpEF, HFmEF, and HFrEF (Table 3). Notably, the relative risk associated with peak VO_2 increased in a graded pattern from HFrEF to HFpEF, with intermediate values in HFmEF. Interactions were noted between HFpEF/HFrEF and peak VO_2 ($P_{interaction}$=0.052) and VE/VCO_2 slope ($P_{interaction}$=0.012) with respect to the composite outcome. Although the absolute event rates of the composite outcome associated with any given value of peak VO_2 and VE/VCO_2 slope were consistently lower in HFpEF compared with HFrEF, the relative risk associated with a unit change in each CPET variable was greater in HFpEF compared with HFrEF (Table 3 and Figure 1). Similar findings were noted when modeling CPET variables as dichotomous variables (Figure 2 and Table S1).

By 2 years post-CPET, 244 patients (25% of the study sample) experienced an incident HF hospitalization, and 475 total HF hospitalizations occurred. Similar to the composite end point, rates of HF hospitalization were similar between the HFmEF and HFpEF groups, and considerably higher in the HFrEF group (Table 3). In multivariable analysis, both peak VO_2 and VE/VCO_2 slope were independently associated with incident HF hospitalization in HFpEF and HFrEF. In contrast, only peak VO_2 was associated with incident HF hospitalization in HFmEF (Table 3). Similar findings were noted for the composite of incident HF hospitalization, death, transplant, or LVAD implantation at 2 years post-CPET (Table S2). Interactions between HFpEF/HFrEF and peak VO_2 ($P_{interaction}$=0.003) and VE/VCO_2 slope ($P_{interaction}$=0.019) were noted with respect to the risk of incident HF hospitalization. In addition, the relative risk of incident HF hospitalization associated with a unit change in each CPET variable was greater in HFpEF compared with HFrEF (Table 3 and Figure 1), with similar findings when modeling peak VO_2 and VE/VCO_2 as dichotomous variables (Figure 2 and Table S1). Peak VO_2 was independently associated with total number of HF hospitalizations in all LVEF categories, while VE/VCO_2 was independently associated with total number of HF hospitalizations only in HFrEF (Table 3).

In the HFpEF and HFrEF groups, both peak VO_2 and VE/VCO_2 individually provided incremental prognostic value beyond clinical variables in predicting the composite end

Table 3. Univariate and Multivariable Cox Regression Analyses of CPET Variables for the Composite Outcome (Death, Left Ventricular Assistant Device Implantation or Transplant), Incident HF Hospitalization, and Total HF Hospitalization in Patients With HFrEF, HFmEF, and HFpEF

	HFrEF		HFmEF		HFpEF		*P* for Interaction*	
	LVEF <40% (n=630)		LVEF 40% to 49% (n=144)		LVEF ≥50% (n=195)		HFmEF×HFrEF	HFpEF×HFrEF
Composite outcome†	N=216; Inc. rate=8.8 (95% CI=7.7–10.1)/100 PY		N=19; Inc. rate=2.9 (95% CI=1.9–4.6)/100 PY		N=21; Inc. rate=2.4 (95% CI=1.6–3.7)/100 PY			
	HR (95% CI) (Unadjusted)	HR (95% CI) (Adjusted‡)	HR (95% CI) (Unadjusted)	HR (95% CI) (Adjusted‡)	HR (95% CI) (Unadjusted)	HR (95% CI) (Adjusted‡)		
Peak VO_2 alone	0.85 (0.82–0.88)§	0.87 (0.83–0.90)§	0.80 (0.71–0.90)§	0.79 (0.70–0.90)§	0.75 (0.66–0.85)§	0.76 (0.67–0.87)§	0.17	0.052
VE/VCO_2 slope alone	1.06 (1.05–1.07)§	1.04 (1.03–1.06)§	1.15 (1.08–1.22)§	1.12 (1.05–1.19)§	1.12 (1.07–1.17)§	1.11 (1.06–1.17)§	0.030	0.012
Peak VO_2‖	0.88 (0.85–0.92)§	0.89 (0.85–0.92)§	0.86 (0.75–0.97)§	0.84 (0.74–0.95)§	0.77 (0.67–0.88)§	0.76 (0.66–0.88)§		
VE/VCO_2 slope‖	1.04 (1.03–1.05)§	1.03 (1.01–1.04)§	1.09 (1.02–1.17)§	1.07 (1.00–1.15)§	1.08 (1.02–1.14)§	1.08 (1.03–1.14)§		
Incident HF hospitalization¶	N=200; Inc. rate=27.7 (95% CI=24.1–31.8)/100 PY		N=17; Inc. rate=8.4 (95% CI=6.3–13.3)/100 PY		N=27; Inc. rate=9.2 (95% CI=6.3–13.3)/100 PY			
	HR (95% CI) (Unadjusted)	HR (95% CI) (Adjusted‡)	HR (95% CI) (Unadjusted)	HR (95% CI) (Adjusted‡)	HR (95% CI) (Unadjusted)	HR (95% CI) (Adjusted‡)		
Peak VO_2 alone	0.89 (0.86–0.92)§	0.92 (0.88–0.95)§	0.82 (0.73–0.92)§	0.81 (0.72–0.92)§	0.76 (0.68–0.85)§	0.77 (0.69–0.86)§	0.07	0.003
VE/VCO_2 slope alone	1.06 (1.05–1.08)§	1.04 (1.03–1.06)§	1.08 (1.01–1.15)§	1.05 (0.98–1.13)	1.10 (1.05–1.15)§	1.10 (1.05–1.15)§	0.80	0.019
Peak VO_2‖	0.93 (0.90–0.97)§	0.94 (0.91–0.98)§	0.82 (0.72–0.94)§	0.81 (0.70–0.93)§	0.77 (0.68–0.86)§	0.77 (0.69–0.87)§		
VE/VCO_2 slope‖	1.05 (1.03–1.06)§	1.03 (1.02–1.05)§	1.01 (0.93–1.09)	1.00 (0.92–1.08)	1.07 (1.01–1.12)§	1.07 (1.02–1.13)§		
Total HF hospitalization¶	N=375		N=33		N=67			
	IRR (95% CI) (Unadjusted)	IRR (95% CI) (Adjusted‡)	IRR (95% CI) (Unadjusted)	IRR (95% CI) (Adjusted‡)	IRR (95% CI) (Unadjusted)	IRR (95% CI) (Adjusted‡)		
Peak VO_2 alone	0.89 (0.86–0.93)§	0.91 (0.88–0.95)§	0.77 (0.68–0.88)§	0.79 (0.70–0.90)§	0.68 (0.59–0.78)§	0.69 (0.61–0.79)§	0.035	<0.001
VE/VCO_2 slope alone	1.06 (1.04–1.08)§	1.04 (1.02–1.06)§	1.10 (1.02–1.19)§	1.05 (0.98–1.13)	1.04 (0.99–1.08)	1.03 (0.99–1.08)	0.66	0.91
Peak VO_2‖	0.93 (0.89–0.97)§	0.93 (0.89–0.97)§	0.78 (0.68–0.90)§	0.78 (0.68–0.90)§	0.68 (0.59–0.78)§	0.70 (0.61–0.80)§		
VE/VCO_2 slope‖	1.04 (1.02–1.06)§	1.02 (1.00–1.04)§	1.01 (0.93–1.10)	0.99 (0.91–1.07)	1.00 (0.95–1.05)	1.00 (0.95–1.05)		

HF categories (HFrEF, HFmEF, and HFpEF) are mutually exclusive, and each patient is only in 1 category. CI indicates confidence interval; CPET, cardiopulmonary exercise testing; HF, heart failure; HFmEF, HF with midrange LVEF; HFpEF, HF with preserved LVEF; HFrEF, HF with reduced LVEF; HR, hazard ratio; Inc., Incidence; IRR, incidence rate ratio; LVEF, left ventricular ejection fraction; PY, patient-years; VE/VCO_2, minute ventilation–carbon dioxide production relationship; VO_2, oxygen consumption.

**P* for interaction between HFrEF/HFmEF or HFrEF/HFpEF status and CPET variables regarding the adjusted models.

†The composite outcome was defined as the composite outcome of left ventricular assist device implantation, heart transplantation, or all-cause mortality. Median follow-up for the composite outcome=4.2 [2.8–5.6] y post-CPET.

‡Adjusted for age, sex, ejection fraction, chronic kidney disease, resting heart rate, resting systolic blood pressure, and coronary artery disease.

§*P*<0.05.

‖VE/VCO_2 slope and peak VO_2 were included in the same model.

¶Incident and total HF hospitalization follow-up was assessed up to 2 y post-CPET.

DOI: 10.1161/JAHA.117.006000

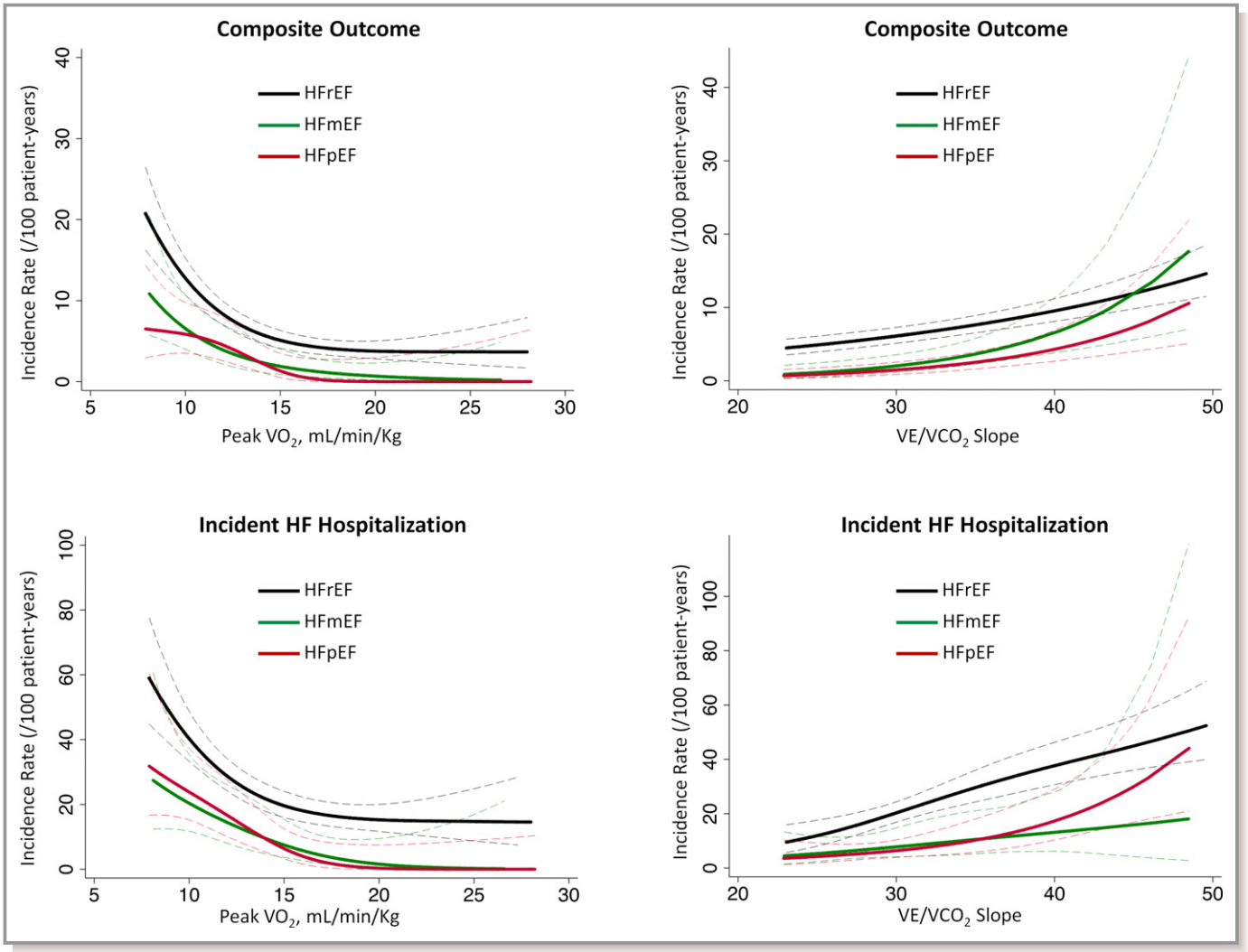


Figure 1. Adjusted incidence rates of the composite outcome and heart failure hospitalization according to peak VO_2 and VE/VCO_2 slope in HFrEF, HFmEF, and HFpEF participants. All analyses were adjusted for age, sex, ejection fraction, chronic kidney disease, resting heart rate, resting systolic blood pressure, and coronary artery disease. Dashed lines indicate the 95% confidence intervals. HF indicates heart failure; HFmEF, HF with midrange ejection fraction; HFpEF, HF with preserved ejection fraction; HFrEF, HF with reduced ejection fraction; VE/VCO_2, minute ventilation–carbon dioxide production relationship; VO_2, oxygen consumption.

point and incident HF hospitalization based on the cross-validated C-statistic, NRI, and IDI (Table 4). The largest improvement in C-statistic and changes in NRI and IDI were observed with the addition of both peak VO_2 and VE/VCO_2 to clinical covariates in the HFpEF and HFrEF groups. In HFmEF patients, CPET variables did not provide incremental prognostic value when assessed by C-statistic, even though there was a trend toward improvement in NRI and IDI when adding peak VO_2 to clinical variables, particularly for incident HF hospitalization.

Sensitivity Analysis

Similar results for predictive modeling and incremental value analysis were observed when percent predicted peak VO_2 based on the Wasserman formula was used instead of peak VO_2 (Tables S3 and S4).

Discussion

Our analysis of the prognostic value of peak VO_2 and VE/VCO_2 slope in HFpEF, HFmEF, and HFrEF is one of the first, to our knowledge, to specifically assess the prognostic relevance of functional capacity and ventilatory efficiency in HFmEF and to quantify their incremental value in HFpEF. Our study has 3 major novel findings. First, both peak VO_2 and VE/VCO_2 slope provide independent and incremental prognostic value for the composite of all-cause death, LVAD implantation or heart transplant, and for incident HF hospitalization in HFpEF. Second, the magnitude of association between peak VO_2 and

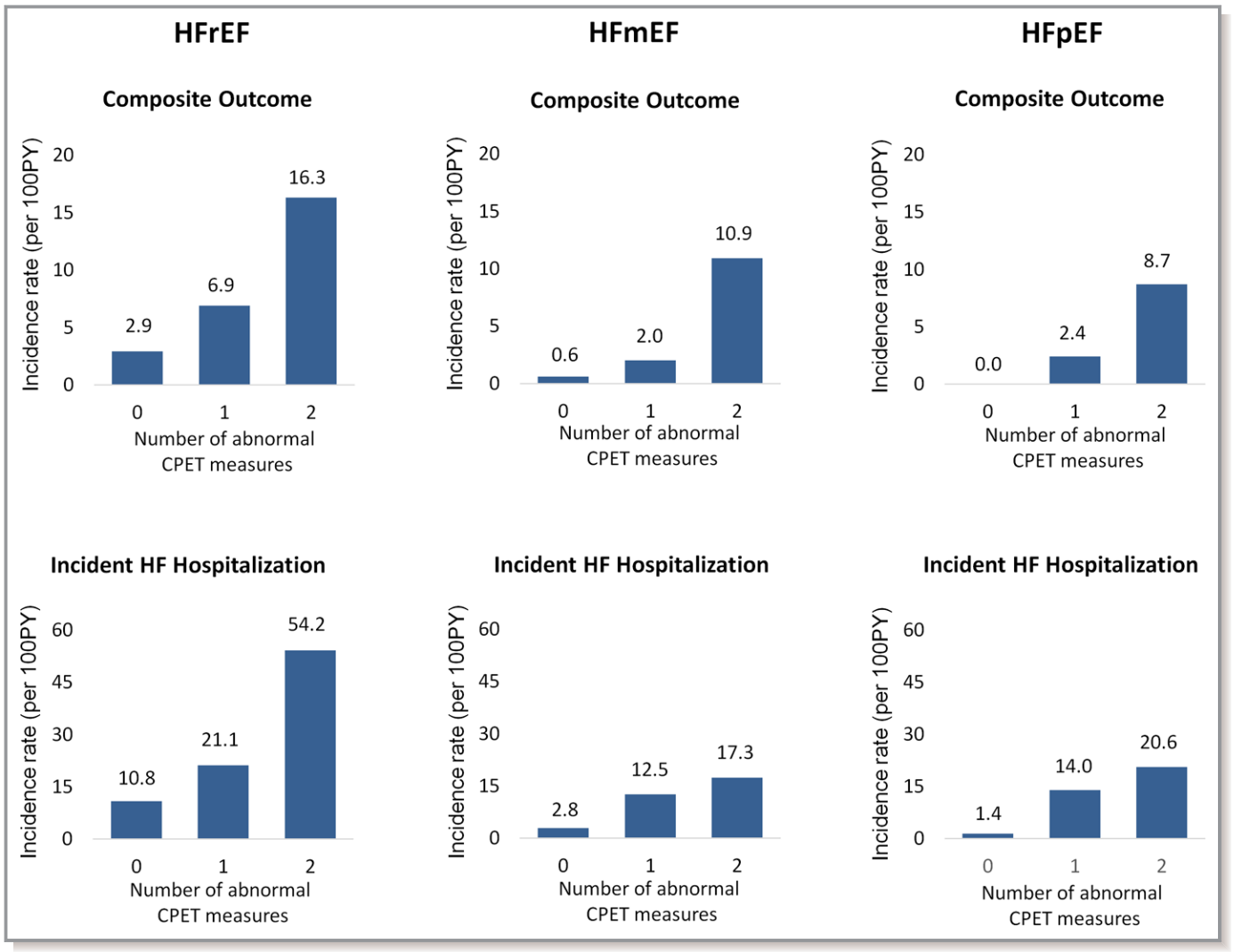


Figure 2. Unadjusted incidence rates of the studied outcomes in HFrEF, HFmEF, and HFpEF patients categorized according to presence of abnormalities in CPET measures. Abnormalities in CPET measures were considered as follows: Peak VO_2 <14 mL/min per kg or VE/VCO_2 slope >30. CPET indicates cardiopulmonary exercise testing; HF, heart failure; HFmEF, HF with midrange ejection fraction; HFpEF, HF with preserved ejection fraction; HFrEF, HF with reduced ejection fraction; PY, patient-years; VE/VCO_2, minute ventilation–carbon dioxide production relationship; VO_2, oxygen consumption.

VE/VCO_2 slope and adverse outcomes was greater in HFpEF compared with HFrEF, such that these CPET variables provided greater risk discrimination in HFpEF compared with HFrEF. Third, the relative risk associated with peak VO_2 for all studied outcomes had intermediate values in HFmEF when compared with HFrEF and HFpEF. These findings support the use CPET as a robust tool for prognostic stratification of HFpEF patients.

Existing studies regarding the prognostic relevance of CPET in HFpEF have demonstrated conflicting results. In 46 patients with LVEF ≥50%, Guazzi et al reported that VE/VCO_2 slope, but not peak VO_2, was associated with all-cause mortality and hospitalization at 1 year.[13] The same group subsequently reported that VE/VCO_2 slope, but not peak VO_2, was associated with cardiac-related death in a sample of 151 HFpEF patients with an average LVEF value of 47.8% and a median follow-up of 13 months.[14] Notably, multivariable adjustment for clinical risk factors was not included in these 2 reports. In a study including 224 HFpEF (LVEF ≥50%) patients with a mean follow-up of 30 months, Yan et al found that VE/VCO_2 slope, but not peak VO_2, was associated with all-cause mortality after adjusting for clinical variables and brain natriuretic peptide levels.[15] In contrast, Shafiq et al found that peak VO_2, but not VE/VCO_2 slope, was associated with all-cause mortality or cardiac transplant after adjusting for age, sex, and β-blockade therapy in their study of 173 HFpEF (LVEF ≥50%) patients followed up for a median of 5.2 years.[16] Our study had more diverse outcomes than previous reports and a larger sample size than most of the former studies.[13–16] In

Table 4. Incremental Value of CPET Parameters in Predicting the Composite Outcome (Death, Left Ventricular Assist Device Implantation, or Transplant) or Incident HF Hospitalization Beyond Clinical Variables in Patients With HFrEF, HFmEF, and HFpEF

Variable	C-Statistic	*P* Value*	IDI (95% CI)	*P* Value*	NRI (95% CI)	*P* Value*
Composite outcome†						
HFrEF (LVEF <40%)						
Clinical	0.72	…				
Clinical+peakVO_2	0.75	0.018	0.077 (0.041–0.115)	<0.001	0.292 (0.197–0.385)	<0.001
Clinical+VE/VCO_2 slope	0.75	0.005	0.041 (0.013–0.070)	0.008	0.208 (0.035–0.309)	0.020
Clinical+peakVO_2+VE/VCO_2 slope	0.76	0.005	0.089 (0.050–0.128)	<0.001	0.266 (0.182–0.376)	<0.001
HFmEF (LVEF 40–49%)						
Clinical	0.74	…				
Clinical+peakVO_2	0.81	0.07	0.070 (−0.020 to 0.217)	0.10	0.317 (−0.211 to 0.621)	0.13
Clinical+VE/VCO_2 slope	0.75	0.22	0.037 (−0.027 to 0.156)	0.25	0.275 (−0.242 to 0.543)	0.23
Clinical+peakVO_2+VE/VCO_2 slope	0.80	0.11	0.084 (−0.020 to 0.254)	0.10	0.338 (−0.161 to 0.646)	0.11
HFpEF (LVEF ≥50%)						
Clinical	0.57	…				
Clinical+peakVO_2	0.75	0.012	0.143 (0.036–0.309)	0.004	0.474 (0.233–0.730)	0.004
Clinical+VE/VCO_2 slope	0.66	0.023	0.067 (0.000–0.210)	0.048	0.317 (0.026–0.566)	0.036
Clinical+peakVO_2+VE/VCO_2 slope	0.80	0.001	0.218 (0.077–0.402)	<0.001	0.639 (0.337–0.824)	0.004
Incident HF hospitalization‡						
HFrEF (LVEF <40%)						
Clinical	0.67	…				
Clinical+peakVO_2	0.69	0.083	0.027 (0.004–0.061)	0.012	0.161 (0.028–0.242)	0.008
Clinical+VE/VCO_2 slope	0.70	0.001	0.034 (0.007–0.066)	0.004	0.163 (0.012–0.281)	0.044
Clinical+peakVO_2+VE/VCO_2 slope	0.70	0.002	0.045 (0.012–0.081)	0.004	0.193 (0.051–0.285)	0.016
HFmEF (LVEF 40–49%)						
Clinical	0.72	…				
Clinical+peakVO_2	0.74	0.54	0.102 (0.002–0.242)	0.036	0.244 (−0.075 to 0.528)	0.09
Clinical+VE/VCO_2 slope	0.68	0.10	0.000 (−0.008 to 0.062)	1.00	−0.002 (−0.163 to 0.269)	1.00
Clinical+peakVO_2+VE/VCO_2 slope	0.72	0.91	0.110 (0.014–0.257)	0.020	0.420 (−0.001 to 0.620)	0.052
HFpEF (LVEF ≥50%)						
Clinical	0.61	…				
Clinical+peakVO_2	0.79	0.007	0.167 (0.043–0.339)	<0.001	0.446 (0.188–0.645)	0.008
Clinical+VE/VCO_2 slope	0.69	0.048	0.075 (0.004–0.199)	0.024	0.347 (−0.009 to 0.515)	0.052
Clinical+peakVO_2+VE/VCO_2 slope	0.81	0.001	0.223 (0.113–0.395)	<0.001	0.522 (0.311–0.689)	<0.001

Clinical variables were the following: age, sex, LVEF, chronic kidney disease, resting systolic blood pressure, resting heart rate, and coronary artery disease. CI indicates confidence interval; CPET, cardiopulmonary exercise testing; HF, heart failure; HFmEF, HF with midrange LVEF; HFpEF, HF with preserved LVEF; HFrEF, HF with reduced LVEF; IDI, integrated diagnostic improvement; LVEF, left ventricular ejection fraction; NRI, net reclassification improvement; VE/VCO_2, minute ventilation–carbon dioxide production relationship; VO_2, oxygen consumption.

**P* values compared with the model containing solely clinical variables.

†C-statistic values were calculated considering the whole follow-up period for the composite outcome (median=4.2 [2.8–5.6]) y, while continuous NRI and IDI were estimated at 4 y post-CPET.

‡All HF incident hospitalization analyses were limited to 2 y of follow-up after the CPET date.

multivariable analysis including a greater number of relevant clinical covariates than previous studies,[15,16] both VE/VCO_2 slope and peak VO_2 (absolute or percent of predicted) were independently prognostic in HFpEF patients. Beyond demonstrating an independent association with HF morbidity and mortality, VE/VCO_2 slope and peak VO_2 provided incremental prognostic value beyond relevant clinical covariates, as assessed by C-statistic, NRI and IDI,

demonstrating that both measures provide complementary prognostic information in HFpEF.

Consistent with prior reports,[13] at any given value of peak VO_2 or VE/VCO_2 slope, HFrEF patients demonstrated higher event rates than HFpEF patients for all study outcomes. However, in Cox regression analysis, the magnitude of association between peak VO_2 and VE/VCO_2 slope and outcomes is greater in HFpEF compared with HFrEF, suggesting that peak VO_2 and VE/VCO_2 slope may offer greater prognostic discrimination in HFpEF than HFrEF. The reasons for these differences are not certain, but may relate to the greater clinical and pathophysiologic heterogeneity characterizing the HFpEF syndrome relative to HFrEF.[6] Conversely, the lower event rates in HFpEF participants than in HFrEF participants, particularly at the highest peak VO_2 and the lowest VE/VCO_2 slope values, may contribute to the greater relative risk associated with these measures in HFpEF compared with HFrEF. Indeed, the absolute difference in event rates was higher in HFrEF than in HFpEF when comparing high versus low peak VO_2 and VE/VCO_2 slope modeled dichotomously. However, these findings demonstrate the ability of peak VO_2 and VE/VCO_2 slope to identify patients with HFpEF with very low risk (composite outcome in 0.0% annually and HF hospitalization in 1.4% annually with peak VO_2 >14 mL/min per kg and VE/VCO_2 slope <30) and very high risk (composite outcome in 8.7% annually and HF hospitalization in 20.6% annually with both CPET measures abnormal). This degree of risk discrimination is particularly impressive when compared with other routinely used approaches to risk stratification in HFpEF. For example, echocardiographic abnormalities of left ventricular hypertrophy, left atrial enlargement and pulmonary hypertension, or elevated circulating natriuretic peptide levels (NT-proBNP >339 pg/mL) have been associated with 1.5- to 2.5-fold higher risk of adverse outcomes in HFpEF populations,[23–25] strengthening the notion that CPET measures are a robust tool for prognostic stratification in HFpEF. Further studies may be necessary to assess whether peak VO_2 and VE/VCO_2 slope are CPET measures that should be systematically incorporated into decision algorithms for clinicians aiming to stratify risk and prognosis in HF patients across the LVEF spectrum.

Recent recommendations have defined a third HF category, HFmEF, comprising patients with LVEF ranging from 40% to 49%.[8] Our analysis, one of the first to our knowledge to specifically interrogate HFmEF relative to HFpEF and HFrEF, demonstrates that clinical features of this group are generally intermediate between those of HFpEF and HFrEF, while CPET performance metrics of HFmEF more closely approximate to HFpEF patients. Notably, the relative risk associated with peak VO_2 for all studied outcomes had intermediate values in HFmEF when compared with HFrEF and HFpEF. In contrast, VE/VCO_2 slope—which was robustly associated with the composite outcome and incident HF hospitalization in both HFrEF and HFpEF—was associated with the composite outcome, but tended to show a neutral association with incident HF hospitalization in HFmEF in fully adjusted analysis. The reasons for this are unclear, but our midrange LVEF sample size was relatively small, and our power may therefore have been limited. However, for recurrent HF hospitalization, effect estimates were clearly neutral in HFmEF, making power alone an unlikely explanation. Further studies in larger samples are required to confirm and further clarify these observations.

This study has several limitations. First, this is an observational study, and thus we cannot exclude the possibility of residual confounding of the observed associations between peak VO_2, VE/VCO_2 slope, and clinical outcomes. Second, our study population consisted of patients referred for CPET at a tertiary medical center, who may not be representative of the overall HF population, potentially limiting the generalizability of our results. However, the average values of peak VO_2 and VE/VCO_2 slope in our population were similar to those reported in other HFrEF and HFpEF populations of comparable age,[13,16,26,27] suggesting that our HF sample had functional capacity measures that reflected those commonly seen in standard practice. Additionally, the rates of both mortality and HF hospitalization in our sample of HFpEF subjects were similar to those reported in HFpEF clinical trials.[28,29] Third, LVAD implantation, heart transplantation, and HF hospitalization data were obtained by review of Brigham and Women's Hospital charts, which could have led to underestimation of these outcomes. However, the frequency of these events occurring at a referral institution different from where they are being longitudinally followed is usually low. Fourth, natriuretic peptides levels, which have known prognostic relevance in HF, were not available or uniformly assessed in our population. Fifth, we did not routinely collect measures of subjective effort in our CPET database. However, we objectively measured subject effort by peak respiratory exchange ratio, which is considered both accurate and reliable.[1] Sixth, LVEF was included as a covariate in all multivariate models, which might raise the possibility of multicollinearity, given that HF categories were derived based on LVEF. We included LVEF as a covariate because this variable showed an inverse relationship with the studied outcomes even within HF categories (Figure S1). This approach is concordant with other reports that also included LVEF in multivariate models when evaluating outcomes in HF patients stratified by LVEF categories.[30,31] Importantly, the exclusion of LVEF from our multivariate models did not change the observed associations between CPET variables and the studied outcomes (Table S5).

Conclusions

Peak VO_2 is robustly predictive of worse prognosis in HFpEF, HFmEF, and HFrEF. Among patients with HFpEF, both peak VO_2 and VE/VCO_2 slope provided incremental prognostic value beyond relevant clinical covariates for the composite of all-cause death, LVAD implantation or heart transplant, and for incident HF hospitalization. Notably, the magnitude of association between peak VO_2 and VE/VCO_2 slope and adverse outcomes was greater in HFpEF compared with HFrEF, such that these CPET variables provided greater risk discrimination in HFpEF compared with HFrEF. Together these findings support the notion that CPET is a robust albeit underutilized tool for risk stratification in HFpEF.

Sources of Funding

This work was supported by NHLBI grant K08HL116792 (Shah), AHA grant 14CRP20380422 (Shah), a Watkins Discovery Award from the Brigham and Women's Heart and Vascular Center (Shah), and the Brazilian National Council for Scientific and Technological Development grant 249481/2013-8 (Nadruz).

Disclosures

Dr Shah reports receiving research support from Novartis and Gilead, and consulting fees from Myocardia. The other authors have nothing to disclose.

References

1. Balady GJ, Arena R, Sietsema K, Myers J, Coke L, Fletcher GF, Forman D, Franklin B, Guazzi M, Gulati M, Keteyian SJ, Lavie CJ, Macko R, Mancini D, Milani RV; American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee of the Council on Clinical Cardiology; Council on Epidemiology and Prevention; Council on Peripheral Vascular Disease; Interdisciplinary Council on Quality of Care and Outcomes Research. Clinician's Guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. *Circulation*. 2010;122:191–225.
2. Arena R, Guazzi M, Cahalin LP, Myers J. Revisiting cardiopulmonary exercise testing applications in heart failure: aligning evidence with clinical practice. *Exerc Sport Sci Rev*. 2014;42:153–160.
3. Smith GL, Masoudi FA, Vaccarino V, Radford MJ, Krumholz HM. Outcomes in heart failure patients with preserved ejection fraction: mortality, readmission, and functional decline. *J Am Coll Cardiol*. 2003;41:1510–1518.
4. Burkhoff D. Mortality in heart failure with preserved ejection fraction: an unacceptably high rate. *Eur Heart J*. 2012;33:1718–1720.
5. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med*. 2006;355:251–259.
6. Shah AM. Ventricular remodeling in heart failure with preserved ejection fraction. *Curr Heart Fail Rep*. 2013;10:341–349.
7. Samson R, Jaiswal A, Ennezat PV, Cassidy M, Le Jemtel TH. Clinical phenotypes in heart failure with preserved ejection fraction. *J Am Heart Assoc*. 2016;5:e002477. DOI: 10.1161/JAHA.115.002477.
8. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P; Authors/Task Force Members. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2016;37:2129–2200.
9. Guazzi M. Cardiopulmonary exercise testing in heart failure preserved ejection fraction: time to expand the paradigm in the prognostic algorithm. *Am Heart J*. 2016;174:164–166.
10. Nedeljkovic I, Banovic M, Stepanovic J, Giga V, Djordjevic-Dikic A, Trifunovic D, Nedeljkovic M, Petrovic M, Dobric M, Dikic N, Zlatar M, Beleslin B. The combined exercise stress echocardiography and cardiopulmonary exercise test for identification of masked heart failure with preserved ejection fraction in patients with hypertension. *Eur J Prev Cardiol*. 2016;23:71–77.
11. Edelmann F, Wachter R, Schmidt AG, Kraigher-Krainer E, Colantonio C, Kamke W, Duvinage A, Stahrenberg R, Durstewitz K, Löffler M, Düngen HD, Tschöpe C, Herrmann-Lingen C, Halle M, Hasenfuss G, Gelbrich G, Pieske B; Aldo-DHF Investigators. Effect of spironolactone on diastolic function and exercise capacity in patients with heart failure with preserved ejection fraction: the Aldo-DHF randomized controlled trial. *JAMA*. 2013;309:781–791.
12. Redfield MM, Chen HH, Borlaug BA, Semigran MJ, Lee KL, Lewis G, LeWinter MM, Rouleau JL, Bull DA, Mann DL, Deswal A, Stevenson LW, Givertz MM, Ofili EO, O'Connor CM, Felker GM, Goldsmith SR, Bart BA, McNulty SE, Ibarra JC, Lin G, Oh JK, Patel MR, Kim RJ, Tracy RP, Velazquez EJ, Anstrom KJ, Hernandez AF, Mascette AM, Braunwald E; RELAX Trial. Effect of phosphodiesterase-5 inhibition on exercise capacity and clinical status in heart failure with preserved ejection fraction: a randomized clinical trial. *JAMA*. 2013;309:1268–1277.
13. Guazzi M, Myers J, Arena R. Cardiopulmonary exercise testing in the clinical and prognostic assessment of diastolic heart failure. *J Am Coll Cardiol*. 2005;46:1883–1890.
14. Guazzi M, Myers J, Peberdy MA, Bensimhon D, Chase P, Arena R. Exercise oscillatory breathing in diastolic heart failure: prevalence and prognostic insights. *Eur Heart J*. 2008;29:2751–2759.
15. Yan J, Gong SJ, Li L, Yu HY, Dai HW, Chen J, Tan CW, Xv QH, Cai GL. Combination of B-type natriuretic peptide and minute ventilation/carbon dioxide production slope improves risk stratification in patients with diastolic heart failure. *Int J Cardiol*. 2013;162:193–198.
16. Shafiq A, Brawner CA, Aldred HA, Lewis B, Williams CT, Tita C, Schairer JR, Ehrman JK, Velez M, Selektor Y, Lanfear DE, Keteyian SJ. Prognostic value of cardiopulmonary exercise testing in heart failure with preserved ejection fraction. The Henry Ford HospITal CardioPulmonary EXercise Testing (FIT-CPX) project. *Am Heart J*. 2016;174:167–172.
17. Nadruz W Jr, West E, Santos M, Skali H, Groarke JD, Forman DE, Shah AM. Heart failure and midrange ejection fraction: implications of recovered ejection fraction for exercise tolerance and outcomes. *Circ Heart Fail*. 2016;9:e002826.
18. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF III, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150:604–612.
19. Hansen JE, Sue DY, Wasserman K. Predicted values for clinical exercise testing. *Am Rev Respir Dis*. 1984;129(2 pt 2):S49–S55.
20. Astrand I. Aerobic work capacity in men and women with special reference to age. *Acta Physiol Scand Suppl*. 1960;49:1–92.
21. Brubaker PH, Kitzman DW. Chronotropic incompetence: causes, consequences, and management. *Circulation*. 2011;123:1010–1020.
22. Uno H, Tian L, Cai T, Kohane IS, Wei LJ. A unified inference procedure for a class of measures to assess improvement in risk prediction systems with survival data. *Stat Med*. 2013;32:2430–2442.
23. Anand IS, Rector TS, Cleland JG, Kuskowski M, McKelvie RS, Persson H, McMurray JJ, Zile MR, Komajda M, Massie BM, Carson PE. Prognostic value of baseline plasma amino-terminal pro-brain natriuretic peptide and its interactions with irbesartan treatment effects in patients with heart failure and preserved ejection fraction: findings from the I-PRESERVE trial. *Circ Heart Fail*. 2011;4:569–577.
24. Zile MR, Gottdiener JS, Hetzel SJ, McMurray JJ, Komajda M, McKelvie R, Baicu CF, Massie BM, Carson PE; I-PRESERVE Investigators. Prevalence and significance of alterations in cardiac structure and function in patients with heart failure and a preserved ejection fraction. *Circulation*. 2011;124:2491–2501.
25. Shah AM, Claggett B, Sweitzer NK, Shah SJ, Anand IS, O'Meara E, Desai AS, Heitner JF, Li G, Fang J, Rouleau J, Zile MR, Markov V, Ryabov V, Reis G, Assmann SF, McKinlay SM, Pitt B, Pfeffer MA, Solomon SD. Cardiac structure and function and prognosis in heart failure with preserved ejection fraction: findings from the echocardiographic study of the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) Trial. *Circ Heart Fail*. 2014;7:740–751.

26. Chase PJ, Kenjale A, Cahalin LP, Arena R, Davis PG, Myers J, Guazzi M, Forman DE, Ashley E, Peberdy MA, West E, Kelly CT, Bensimhon DR. Effects of respiratory exchange ratio on the prognostic value of peak oxygen consumption and ventilatory efficiency in patients with systolic heart failure. *JACC Heart Fail*. 2013;1:427–432.

27. Keteyian SJ, Patel M, Kraus WE, Brawner CA, McConnell TR, Piña IL, Leifer ES, Fleg JL, Blackburn G, Fonarow GC, Chase PJ, Piner L, Vest M, O'Connor CM, Ehrman JK, Walsh MN, Ewald G, Bensimhon D, Russell SD; HF-ACTION Investigators. Variables measured during cardiopulmonary exercise testing as predictors of mortality in chronic systolic heart failure. *J Am Coll Cardiol*. 2016;67:780–789.

28. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, Michelson EL, Olofsson B, Ostergren J; CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. *Lancet*. 2003;362:777–781.

29. Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, Anderson S, Donovan M, Iverson E, Staiger C, Ptaszynska A; I-PRESERVE Investigators. Irbesartan in patients with heart failure and preserved ejection fraction. *N Engl J Med*. 2008;359:2456–2467.

30. Gupta DK, Shah AM, Castagno D, Takeuchi M, Loehr LR, Fox ER, Butler KR, Mosley TH, Kitzman DW, Solomon SD. Heart failure with preserved ejection fraction in African Americans: the ARIC (Atherosclerosis Risk In Communities) study. *JACC Heart Fail*. 2013;1:156–163.

31. Yanagihara K, Kinugasa Y, Sugihara S, Hirai M, Yamada K, Ishida K, Kato M, Yamamoto K. Discharge use of carvedilol is associated with higher survival in Japanese elderly patients with heart failure regardless of left ventricular ejection fraction. *J Cardiovasc Pharmacol*. 2013;62:485–490.

SUPPLEMENTAL MATERIAL

Table S1. Unadjusted incidence rates, rate differences and adjusted hazard ratios of the studied outcomes in HFpEF and HFrEF patients categorized according to presence of abnormalities in CPET measures.

	Composite endpoint				**Incident HF hospitalization**			
	HFrEF (LVEF <40%)				**HFrEF (**LVEF <40%)			
Number of abnormal CPET measures	*N of events/ total N*	*Incidence rate (95%CI)*	*Rate difference (95%CI)*	*Hazard Ratio (95%CI)**	*N of events/ total N*	*Incidence rate (95%CI)*	*Rate difference (95%CI)*	*Hazard Ratio (95%CI)**
0	20/150	2.9 (1.8-4.4)	Ref	Ref	24/150	10.8 (7.3-16.2)	Ref	Ref
1	65/222	6.9 (5.4-8.8)	4.0 (2.0-6.2)	1.78 (1.06-2.98)	61/222	21.1 (16.4-27.1)	10.3 (3.4-17.1)	1.47 (0.90-2.39)
2	131/258	16.3 (13.7-19.3)	13.4 (10.4-16.5)	3.28 (1.98-5.44)	115/258	54.2 (45.2-65.1)	43.4 (32.6-54.2)	2.75 (1.71-4.42)
	HFmEF (LVEF 40-49%)				**HFmEF (**LVEF 40-49%)			
Number of abnormal CPET measures	*N of events/ total N*	*Incidence rate (95%CI)*	*Rate difference (95%CI)*	*Hazard Ratio (95%CI)**	*N of events/ total N*	*Incidence rate (95%CI)*	*Rate difference (95%CI)*	*Hazard Ratio (95%CI)**
0	2/70	0.6 (0.1-2.4)	Ref	Ref	3/70	2.8 (0.9-8.8)	Ref	Ref
1	4/41	2.0 (0.8-5.4)	1.4 (-0.7-3.6)	3.20 (0.58-17.55)	7/41	12.5 (6.0-26.3)	9.7 (-0.1-19.5)	4.07 (1.05-15.58)
2	13/33	10.9 (6.3-18.8)	10.3 (4.3-16.3)	13.97 (3.07-63.48)	7/33	17.3 (8.2-36.2)	14.4 (1.2-27.6)	4.34 (1.09-17.21)
	HFpEF (LVEF ≥50%)				**HFpEF (**LVEF ≥50%)			
Number of abnormal CPET measures	*N of events/ total N*	*Incidence rate (95%CI)*	*Rate difference (95%CI)*	*Hazard Ratio (95%CI)**	*N of events/ total N*	*Incidence rate (95%CI)*	*Rate difference (95%CI)*	*Hazard Ratio (95%CI)**

0	0/92	0.0 (0.0-0.0)	Ref	Ref	2/92	1.4 (0.3-5.4)	Ref	Ref
1	6/55	2.4 (1.1-5.4)	2.4 (1.1-5.4)	–	11/55	14.0 (7.7-25.3)	12.6 (4.2-21.1)	10.19 (2.23-46.43)
2	15/48	8.7 (5.2-14.4)	8.7 (5.2-14.4)	–	14/48	20.6 (12.2-34.7)	19.2 (8.3-30.2)	12.65 (2.82-56.84)

Legend. Abnormalities in CPET measures were considered as: Peak VO_2<14 mL/min/Kg or VE/VCO_2 slope>30. The composite outcome was defined as the composite outcome of left ventricular assistant device implantation, heart transplantation or all-cause mortality. Incidence rates are presented in 100 patient-years. Similar findings were observed using a cut off of 35 for VE/VCO_2 slope (data not shown).

* Adjusted for age, sex, LVEF, chronic kidney disease, resting systolic blood pressure, resting heart rate, and coronary artery disease.

CPET – cardiopulmonary exercise testing; HF – heart failure; HFmEF – HF with mid-range ejection fraction; HFpEF – HF with preserved ejection fraction; HFrEF – HF with reduced ejection fraction; VE/VCO_2 - minute ventilation-carbon dioxide production relationship; VO_2 – oxygen consumption;

Table S2. Univariate and multivariable Cox regression analyses of CPET variables for the composite of incident HF hospitalization or composite outcome up to two years post-CPET in HFrEF, HFmEF and HFpEF patients.

	HFrEF LVEF <40% (n=630)		HFmEF LVEF 40-49% (n=144)		HFpEF LVEF ≥50% (n=195)		P for interaction§ HFmEF X HFrEF	P for interaction§ HFpEF X HFrEF
	N=210; Inc. rate=29.7 (95%CI=25.9-34.0)/100PY		N=19; Inc. rate=9.5 (95%CI=6.1-14.9)/100PY		N=27; Inc. rate=9.2 (95%CI=6.3-13.3)/100PY			
Composite outcome + incident HF hospitalization ‡	**HR (95% CI) (Unadjusted)**	**HR (95% CI) (Adjusted†)**	**HR (95% CI) (Unadjusted)**	**HR (95% CI) (Adjusted†)**	**HR (95% CI) (Unadjusted)**	**HR (95% CI) (Adjusted†)**		
Peak VO_2 alone	0.88 (0.85-0.92)*	0.91 (0.88-0.94)*	0.84 (0.76-0.94)*	0.84 (0.75-0.93)*	0.76 (0.68-0.85)*	0.77 (0.69-0.86)*	0.16	0.004
VE/VCO_2 slope alone	1.06 (1.05-1.08)*	1.04 (1.03-1.06)*	1.08 (1.01-1.15)*	1.06 (0.99-1.13)	1.10 (1.05-1.15)*	1.10 (1.05-1.16)*	0.74	0.020
Peak VO_2**	0.93 (0.89-0.96)*	0.94 (0.90-0.97)*	0.85 (0.76-0.96)*	0.84 (0.73-0.98)*	0.77 (0.68-0.86)*	0.71 (0.61-0.82)*		
VE/VCO_2 slope**	1.05 (1.03-1.06)*	1.04 (1.02-1.05)*	1.02 (0.94-1.10)*	1.01 (0.94-1.09)	1.07 (1.01-1.12)*	1.07 (1.02-1.13)*		

Legend. * $p<0.05$. † Adjusted for age, sex, ejection fraction, chronic kidney disease, resting heart rate, resting systolic blood pressure, and coronary artery disease. ‡ Follow-up was assessed up to 2 years post-CPET.

** VE/VCO_2 slope and peak VO_2 were included in the same model.

§ P for interaction between HFrEF/HFmEF or HFrEF/HFpEF status and CPET variables regarding the adjusted models.

CI – confidence interval; CPET – cardiopulmonary exercise testing; HF – heart failure; HFmEF – HF with mid-range LVEF; HFpEF – HF with preserved LVEF; HFrEF – HF with reduced LVEF; HR – hazard ratio; LVEF- left ventricular ejection fraction; PY – patient-years; VE/VCO_2 – minute ventilation-carbon dioxide production relationship; VO_2 – oxygen consumption.

Table S3. Univariate and multivariable Cox regression analyses of CPET variables (% of predicted peak VO_2 and VE/VCO_2 slope) for the composite outcome (death, left ventricular assistant device implantation or transplant), incident HF hospitalization and total HF hospitalization in patients with HFrEF, HFmEF and HFpEF.

	HFrEF LVEF <40% (n=630)		HFmEF LVEF 40-49% (n=144)		HFpEF LVEF ≥50% (n=195)		P for interaction§ HFmEF X HFrEF	P for interaction§ HFpEF X HFrEF
Composite outcome‡	N=216; Inc. rate=8.8 (95%CI=7.7-10.1)/100PY		N=19; Inc. rate=2.9 (95%CI=1.9-4.6)/100PY		N=21; Inc. rate=2.4 (95%CI=1.6-3.7)/100PY			
	HR (95% CI) (Unadjusted)	**HR (95% CI) (Adjusted†)**	**HR (95% CI) (Unadjusted)**	**HR (95% CI) (Adjusted†)**	**HR (95% CI) (Unadjusted)**	**HR (95% CI) (Adjusted†)**		
% pred. Peak VO_2 alone	0.96 (0.94-0.96)*	0.96 (0.95-0.97)*	0.95 (0.92-0.98)*	0.96 (0.93-0.99)*	0.94 (0.91-0.96)*	0.94 (0.92-0.97)*	0.79	0.25
VE/VCO_2 slope alone	1.06 (1.05-1.07)*	1.04 (1.03-1.06)*	1.15 (1.08-1.22)*	1.12 (1.05-1.19)*	1.12 (1.07-1.17)*	1.11 (1.06-1.17)*	0.030	0.012
% pred. Peak VO_2**	0.96 (0.95-0.97)*	0.97 (0.96-0.98)*	0.98 (0.95-1.01)*	0.97 (0.94-1.00)	0.95 (0.92-0.98)*	0.95 (0.93-0.98)*		
VE/VCO_2 slope**	1.04 (1.02-1.05)*	1.02 (1.01-1.04)*	1.12 (1.04-1.20)*	1.08 (1.01-1.13)*	1.08 (1.02-1.13)*	1.07 (1.02-1.13)*		
Incident HF hospitalization#	N=200; Inc. rate=27.7 (95%CI=24.1-31.8)/100PY		N=17; Inc. rate=8.4 (95%CI=6.3-13.3)/100PY		N=27; Inc. rate=9.2 (95%CI=6.3-13.3)/100PY			
	HR (95% CI) (Unadjusted)	**HR (95% CI) (Adjusted†)**	**HR (95% CI) (Unadjusted)**	**HR (95% CI) (Adjusted†)**	**HR (95% CI) (Unadjusted)**	**HR (95% CI) (Adjusted†)**		

% pred. Peak VO_2 alone	0.97 (0.96-0.98)*	0.98 (0.97-0.99)*	0.96 (0.93-0.99)*	0.96 (0.93-0.99)*	0.94 (0.92-0.97)*	0.95 (0.93-0.97)*	0.28	0.045
VE/VCO_2 slope alone	1.06 (1.05-1.08)*	1.04 (1.03-1.06)*	1.08 (1.01-1.15)*	1.05 (0.98-1.13)	1.10 (1.05-1.15)*	1.10 (1.05-1.15)*	0.80	0.019
% pred. Peak VO_2**	0.98 (0.97-0.99)*	0.98 (0.97-0.99)*	0.96 (0.93-0.99)*	0.96 (0.93-0.99)*	0.95 (0.93-0.97)*	0.96 (0.93-0.98)*		
VE/VCO_2 slope**	1.05 (1.03-1.06)*	1.03 (1.01-1.05)*	1.04 (0.96-1.12)	1.01 (0.94-1.09)	1.06 (1.01-1.11)*	1.06 (1.01-1.12)*		
	N=375		N=33		N=67			
Total HF hospitalization[#]	**IRR (95% CI) (Unadjusted)**	**IRR (95% CI) (Adjusted†)**	**IRR (95% CI) (Unadjusted)**	**IRR (95% CI) (Adjusted†)**	**IRR (95% CI) (Unadjusted)**	**IRR (95% CI) (Adjusted†)**		
% pred. Peak VO_2 alone	0.97 (0.96-0.98)*	0.98 (0.97-0.99)*	0.95 (0.92-0.98)*	0.96 (0.93-0.98)*	0.93 (0.90-0.95)*	0.94 (0.91-0.96)*	0.22	0.004
VE/VCO_2 slope alone	1.06 (1.04-1.08)*	1.04 (1.02-1.06)*	1.10 (1.02-1.19)*	1.05 (0.98-1.13)	1.04 (0.99-1.08)	1.03 (0.99-1.08)*	0.66	0.91
% pred. Peak VO_2**	0.98 (0.97-0.99)*	0.98 (0.97-0.99)*	0.96 (0.93-0.99)*	0.96 (0.93-0.99)*	0.93 (0.90-0.95)*	0.94 (0.91-0.96)*		
VE/VCO_2 slope**	1.04 (1.02-1.06)*	1.02 (1.00-1.04)	1.05 (0.97-1.13)	1.00 (0.93-1.08)	1.00 (0.95-1.04)	0.99 (0.94-1.04)		

Legend. * $p<0.05$.

† Adjusted for age, sex, ejection fraction, chronic kidney disease, resting heart rate, resting systolic blood pressure, and coronary artery disease.

‡ The composite outcome was defined as the composite outcome of left ventricular assistant device implantation, heart transplantation or all-cause mortality. Median follow up for the composite outcome = 4.2 [2.8 – 5.6] years post-CPET.

[#] Incident and total HF hospitalization follow-up was assessed up to 2 years post-CPET.

** VE/VCO_2 slope and peak VO_2 were included in the same model.

§ P for interaction between HFrEF/HFmEF or HFrEF/HFpEF status and CPET variables regarding the adjusted models.

CI – confidence interval; CPET – cardiopulmonary exercise testing; HF – heart failure; HFmEF – HF with mid-range LVEF; HFpEF – HF with preserved LVEF; HFrEF – HF with reduced LVEF; HR – hazard ratio; IRR – incidence rate ratio; LVEF- left ventricular ejection fraction; PY – patient-years; VE/VCO_2 – minute ventilation-carbon dioxide production relationship; VO_2 – oxygen consumption.

Table S4. Incremental value of CPET variables (% of predicted peak VO_2 and VE/VCO_2 slope) in predicting the composite outcome (death, left ventricular assistant device implantation or transplant) or incident HF hospitalization beyond clinical variables in patients with HFrEF, HFmEF and HFpEF.

Variable	C-statistic	P value*	IDI (95% CI)	P value*	NRI (95% CI)	P value*
Composite outcome†						
HFrEF (LVEF<40%)						
Clinical	0.72	---				
Clinical + % pred. peakVO_2	0.76	0.001	0.081 (0.041-0.122)	<0.001	0.342 (0.237-0.419)	<0.001
Clinical + VE/VCO_2 slope	0.75	0.005	0.041 (0.013-0.070)	0.008	0.208 (0.035-0.309)	0.020
Clinical + % pred. peakVO_2 + VE/VCO_2 slope	0.76	0.001	0.089 (0.050-0.133)	<0.001	0.310 (0.215-0.416)	<0.001
HFmEF (LVEF 40-49%)						
Clinical	0.74	---				
Clinical + % pred. peakVO_2	0.81	0.10	0.077 (-0.005-0.240)	0.07	0.338 (-0.113-0.633)	0.10
Clinical + VE/VCO_2 slope	0.75	0.22	0.037 (-0.027-0.156)	0.25	0.275 (-0.242-0.543)	0.23
Clinical + % pred. peakVO_2 + VE/VCO_2 slope	0.80	0.14	0.078 (-0.016-0.246)	0.09	0.348 (-0.062-0.642)	0.07
HFpEF (LVEF≥50%)						
Clinical	0.57	---				
Clinical + % pred. peakVO_2	0.73	0.013	0.163 (0.023-0.328)	0.012	0.437 (0.135-0.676)	0.012
Clinical + VE/VCO_2 slope	0.66	0.023	0.067 (0.000-0.210)	0.048	0.317 (0.026-0.566)	0.036
Clinical + % pred. peakVO_2 + VE/VCO_2 slope	0.75	0.005	0.196 (0.053-0.373)	0.004	0.489 (0.233-0.753)	<0.001
Incident HF Hospitalization‡						

HFrEF (LVEF<40%)						
Clinical	0.67	---				
Clinical + % pred. peakVO_2	0.69	0.049	0.034 (0.006-0.074)	0.008	0.179 (0.046-0.272)	0.016
Clinical + VE/VCO_2 slope	0.70	0.001	0.034 (0.007-0.066)	0.004	0.163 (0.012-0.281)	0.044
Clinical + % pred. peakVO_2 + VE/VCO_2 slope	0.70	0.004	0.048 (0.013-0.089)	0.004	0.176 (0.069-0.300)	0.012
HFmEF (LVEF 40-49%)						
Clinical	0.72	---				
Clinical + % pred. peakVO_2	0.73	0.80	0.076 (-0.005-0.204)	0.07	0.158 (-0.154-0.509)	0.22
Clinical + VE/VCO_2 slope	0.68	0.10	0.000 (-0.008-0.062)	1.00	-0.002 (-0.163-0.269)	1.00
Clinical + % pred. peakVO_2 + VE/VCO_2 slope	0.72	0.90	0.094 (0.005-0.250)	0.032	0.377 (-0.061-0.593)	0.10
HFpEF (LVEF≥50%)						
Clinical	0.61	---				
Clinical + % pred. peakVO_2	0.75	0.015	0.094 (0.005-0.258)	0.044	0.404 (0.025-0.610)	0.040
Clinical + VE/VCO_2 slope	0.69	0.048	0.075 (0.004-0.199)	0.024	0.347 (-0.009-0.515)	0.052
Clinical + % pred. peakVO_2 + VE/VCO_2 slope	0.76	0.006	0.137 (0.032-0.317)	0.004	0.427 (0.105-0.600)	0.004

* P-values compared to C-statistic value of the model containing solely clinical variables.
Clinical variables were: age, sex, LVEF, chronic kidney disease, resting systolic blood pressure, resting heart rate, and coronary artery disease.
† C-statistic values were calculated considering the whole follow-up period for the composite outcome (median = 4.2 [2.8 – 5.6]) years, while continuous NRI and IDI we estimated at 4 years post-CPET.
‡ All HF incident hospitalization analyses were limited to 2 years of follow-up after the CPET date.
CI – confidence interval; CPET – cardiopulmonary exercise testing; IDI - integrated diagnostic improvement; HF – heart failure; HFmEF – HF with mid-range LVEF; HFpEF – HF with preserved LVEF; HFrEF – HF with reduced LVEF; NRI – net reclassification improvement; LVEF – left ventricular ejection fraction; VE/VCO_2 – minute ventilation-carbon dioxide production relationship; VO_2 – oxygen consumption.

Table S5. Multivariable Cox regression analyses of CPET variables for the composite outcome (death, left ventricular assistant device implantation or transplant), incident HF hospitalization and total HF hospitalization in patients with HFrEF, HFmEF and HFpEF including or not LVEF as a covariate.

	HFrEF LVEF <40% (n=630)		HFmEF LVEF 40-49% (n=144)		HFpEF LVEF ≥50% (n=195)	
Composite outcome‡	N=216; Inc. rate=8.8 (95%CI=7.7-10.1)/100PY		N=19; Inc. rate=2.9 (95%CI=1.9-4.6)/100PY		N=21; Inc. rate=2.4 (95%CI=1.6-3.7)/100PY	
	HR (95% CI) (Model 1)	**HR (95% CI) (Model 2)**	**HR (95% CI) (Model 1)**	**HR (95% CI) (Model 2)**	**HR (95% CI) (Model 1)**	**HR (95% CI) (Model 2)**
Peak VO_2 alone	0.87 (0.83-0.90)*	0.87 (0.83-0.90)*	0.79 (0.70-0.90)*	0.79 (0.70-0.90)*	0.76 (0.67-0.87)*	0.76 (0.67-0.87)*
VE/VCO_2 slope alone	1.04 (1.03-1.06)*	1.05 (1.03-1.06)*	1.12 (1.05-1.19)*	1.12 (1.05-1.19)*	1.11 (1.06-1.17)*	1.11 (1.06-1.17)*
Peak VO_2**	0.89 (0.85-0.92)*	0.88 (0.85-0.92)*	0.84 (0.74-0.95)*	0.84 (0.73-0.95)*	0.76 (0.66-0.88)*	0.77 (0.66-0.88)*
VE/VCO_2 slope**	1.03 (1.01-1.04)*	1.03 (1.02-1.05)*	1.07 (1.00-1.15)*	1.07 (1.00-1.15)*	1.08 (1.03-1.14)*	1.08 (1.02-1.14)*
Incident HF hospitalization#	N=200; Inc. rate=27.7 (95%CI=24.1-31.8)/100PY		N=17; Inc. rate=8.4 (95%CI=6.3-13.3)/100PY		N=27; Inc. rate=9.2 (95%CI=6.3-13.3)/100PY	
	HR (95% CI) (Model 1)	**HR (95% CI) (Model 2)**	**HR (95% CI) (Model 1)**	**HR (95% CI) (Model 2)**	**HR (95% CI) (Model 1)**	**HR (95% CI) (Model 2)**
Peak VO_2 alone	0.92 (0.88-0.95)*	0.91 (0.88-0.95)*	0.81 (0.72-0.92)*	0.81 (0.72-0.92)*	0.77 (0.69-0.86)*	0.77 (0.69-0.86)*

VE/VCO_2 slope alone	1.04 (1.03-1.06)*	1.05 (1.03-1.06)*	1.05 (0.98-1.13)	1.05 (0.98-1.13)	1.10 (1.05-1.15)*	1.10 (1.05-1.15)*
Peak VO_2**	0.94 (0.91-0.98)*	0.94 (0.90-0.98)*	0.81 (0.70-0.93)*	0.81 (0.70-0.93)*	0.77 (0.69-0.87)*	0.77 (0.69-0.87)*
VE/VCO_2 slope**	1.03 (1.02-1.05)*	1.04 (1.02-1.05)*	1.00 (0.92-1.08)	1.00 (0.92-1.08)	1.07 (1.02-1.13)*	1.07 (1.01-1.13)*
	N=375		N=33		N=67	
Total HF hospitalization#	**IRR (95% CI) (Model 1)**	**IRR (95% CI) (Model 2)**	**IRR (95% CI) (Model 1)**	**IRR (95% CI) (Model 2)**	**IRR (95% CI) (Model 1)**	**IRR (95% CI) (Model 2)**
Peak VO_2 alone	0.91 (0.88-0.95)*	0.91 (0.87-0.94)*	0.79 (0.70-0.90)*	0.79 (0.70-0.90)*	0.69 (0.61-0.79)*	0.70 (0.62-0.80)*
VE/VCO_2 slope alone	1.04 (1.02-1.06)*	1.04 (1.02-1.06)*	1.05 (0.98-1.13)	1.06 (0.98-1.14)	1.03 (0.99-1.08)*	1.03 (0.99-1.08)*
Peak VO_2**	0.93 (0.89-0.97)*	0.93 (0.89-0.97)*	0.78 (0.68-0.90)*	0.79 (0.68-0.90)*	0.70 (0.61-0.80)*	0.70 (0.62-0.80)*
VE/VCO_2 slope**	1.02 (1.00-1.04)*	1.03 (1.01-1.05)*	0.99 (0.91-1.07)	0.99 (0.91-1.07)	1.00 (0.95-1.05)	1.00 (0.96-1.05)

Legend. * $p<0.05$.

Model 1 was adjusted for age, sex, LVEF, chronic kidney disease, resting heart rate, resting systolic blood pressure, and coronary artery disease, while Model 2 did not include LVEF as a covariate.

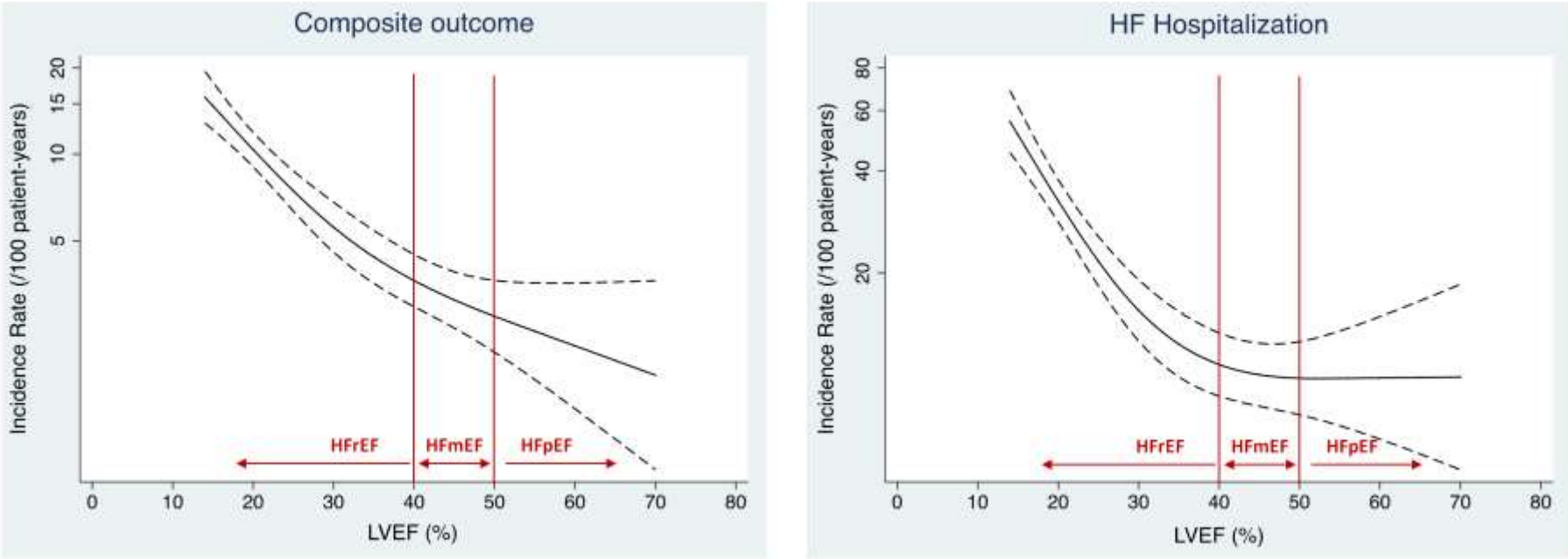
‡ The composite outcome was defined as the composite outcome of left ventricular assistant device implantation, heart transplantation or all-cause mortality. Median follow up for the composite outcome = 4.2 [2.8 – 5.6] years post-CPET.

Incident and total HF hospitalization follow-up was assessed up to 2 years post-CPET.

** VE/VCO_2 slope and peak VO_2 were included in the same model.

CI – confidence interval; CPET – cardiopulmonary exercise testing; HF – heart failure; HFmEF – HF with mid-range LVEF; HFpEF – HF with preserved LVEF; HFrEF – HF with reduced LVEF; HR – hazard ratio; IRR – incidence rate ratio; LVEF- left ventricular ejection fraction; PY – patient-years; VE/VCO_2 – minute ventilation-carbon dioxide production relationship; VO_2 – oxygen consumption.

Figure S1. Unadjusted relationship between incidence of studied outcomes and LVEF assessed by restricted cubic splines.



The 95% confidence intervals are indicated by the dashed lines. HF – heart failure; HFmEF – HF with mid-range LVEF; HFpEF – HF with preserved LVEF; HFrEF – HF with reduced LVEF; LVEF – left ventricular ejection fraction.