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Cardiopulmonary Exercise Testing in the Clinical and Prognostic Assessment of Diastolic Heart Failure

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OBJECTIVES This study sought to define the relative prognostic value of cardiopulmonary exercise testing (CPET) variables in heart failure (HF) patients with preserved versus reduced systolic function.

BACKGROUND Cardiopulmonary exercise testing has an established role in the assessment of patients with systolic heart failure (SHF). Two variables, peak VO_2 and, more recently, the VE/VCO_2 slope, have been shown to be extremely valuable in risk stratification. However, data are lacking in terms of the prognostic value of CPET in patients with diastolic heart failure (DHF).

METHODS A total of 409 HF patients underwent CPET. Patients were divided into three groups according to the following left ventricular ejection fraction (LVEF) cutoffs: ≥40%, ≥45%, and ≥50%. The CPET response and the ability of peak VO_2 and the VE/VCO_2 slope to predict total mortality and hospitalization were examined.

RESULTS At univariate Cox regression analysis, both the peak VO_2 and the VE/VCO_2 slope were significant predictors in SHF and DHF. Multivariate analysis documented a similar prognostic power of VE/VCO_2 slope and peak VO_2 in all SHF groups. Conversely, in DHF patients, VE/VCO_2 slope outnumbered peak VO_2, remaining the only predictor regardless of LVEF. In DHF, the area under the receiver operating characteristic curve for the VE/VCO_2slope identified a cutoff of 32.6 (74% sensitivity, 52% specificity), 33.1 (76% sensitivity, 62% specificity), and 33.3 (97% sensitivity, 40% specificity) for an LVEF cutoff of ≥40%, ≥45%, and ≥50%, respectively.

CONCLUSIONS These results extend the clinical and prognostic applicability of CPET to DHF. An impairment in exercise ventilation rather than peak VO_2 holds clinical and prognostic impact in this increasing subset of patients. (J Am Coll Cardiol 2005;46:1883–90) © 2005 by the American College of Cardiology Foundation

Recent epidemiological studies have provided growing recognition that heart failure (HF) with preserved left ventricular ejection fraction (LVEF) recognized as diastolic heart failure (DHF) is a common and costly clinical entity that is increasing in prevalence (1,2). However, because of the paucity of clinical trials addressing DHF patients, scientific evidence regarding the natural history and clinical features of this syndrome remains limited.

Impaired physical performance is an important hallmark of the early stages of HF (3), and it has recently been suggested that abnormalities in exercise metabolism are part of the clinical scenario that limits exercise tolerance in DHF patients (4). Cardiopulmonary exercise testing (CPET) is the gold-standard technique for the evaluation of putative mechanisms that underlie exercise intolerance in HF (5), and CPET-derived indexes of cardiovascular and respiratory limitation have repeatedly emerged as precise predictors of survival rate (6–12). However, studies assessing the clinical significance and prognostic power of CPET-derived variables have, to this point, exclusively involved patients with depressed LVEF or systolic heart failure (SHF). How and whether CPET may add to the backlog of information regarding DHF patients with preserved LVEF remains unknown.

We therefore designed the current study with two objectives: 1) to explore the prognostic value of CPET variables in the subset of DHF patients, and 2) to better examine the physiological response to exercise in symptomatic patients with DHF.

METHODS

This was a multicenter study consisting of HF patients from the Cardiopulmonary Laboratories at San Paolo Hospital, Milan, Italy; the Virginia Commonwealth University, Richmond, Virginia; and the VA Palo Alto Health Care System and Stanford University, Palo Alto, California. A total of 409 patients with chronic HF were studied during a progressively increasing maximal CPET. Patients who met the Framingham criteria for congestive HF were considered eligible candidates (13). Subjects with significant obstructive lung disease evidenced as a forced expiratory volume in 1 s ≤70% or who were unable to perform a maximal exercise test were excluded from the study. Between 15% and 20% of the whole population were smokers and were similarly distributed across different subgroups. All patients were in New York Heart Association functional class II to III.

As detailed subsequently, diastolic function was assessed by echocardiography and Doppler-derived mitral inflow analysis.

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Abbreviations and Acronyms

CPET = cardiopulmonary exercise test
DHF = diastolic heart failure
HF = heart failure
LVEF = left ventricular ejection fraction
ROC = receiver operating characteristic
SHF = systolic heart failure
V_{CO_2} = carbon dioxide production
V_E = ventilation
V_{O_2} = oxygen uptake

Despite the fact that documentation of a normal systolic function (i.e., preserved LVEF) is part of the definition of DHF, considerable differences in the selection criteria for LVEF cutoffs have been reported across various studies. In a series of reports comparing patients with preserved versus depressed systolic function, the cutoff used was a LVEF ≥40% (14,15). The Working Group of the European Society of Cardiology Guidelines (16) defined systolic function as being normal when LVEF is ≥45%. Subsequent studies aimed at better standardizing the diagnostic criteria of DHF have proposed a cutoff of ≥50% (17–19). It follows that depending on which LVEF cutoff is used, the diagnostic yield of DHF varies greatly. Accordingly, we performed three separate survival analyses based on the three LVEF cutoffs proposed ≥40%, ≥45%, and ≥50%. The LVEF was determined during the initial in-hospital evaluation.

The cause of HF was coronary artery disease in 224 patients, hypertension in 95 patients, and idiopathic cardiomyopathy (cardiac enlargement and absence of a specific reason for that) in the rest of the patients. Other than total mortality, we included hospitalization for cardiac reasons as an end point and performed the analysis considering a follow-up period of one year. Irrespective of etiology, individuals with HF can shift from a stable to an uncompensated status (or vice versa) rather abruptly. Limiting the follow-up period to one year may be clinically optimal given the fluid nature of cardiac function in the HF patient. We recently completed an analysis of the impact of time past CPET on the prognostic characteristics of the V_E/V_{CO_2} slope and peak V_{O_2} in subjects with HF (20). This analysis indicated that the sensitivity for predicting outcomes increased modestly, whereas specificity dramatically decreased for both CPET variables after more than one year after exercise testing. A one-year tracking period may therefore represent an appropriate balance between avoiding outdated information and the economic constraints of multiple exercise tests.

Subjects were followed up for cardiac-related mortality and hospitalization via medical chart review at the respective centers. Cardiac-related mortality was defined as death directly resulting from failure of the cardiac system. An example fitting this definition is myocardial infarction followed by cardiac arrest. Cardiac-related hospitalization was defined as a hospital admission directly resulting from cardiac dysfunction requiring in-patient care. An example fitting this definition is decompensated HF requiring the use of an intravenous inotropic agent. Any death or hospital admission with a cardiac-related discharge diagnosis, confirmed by diagnostic test or autopsy, was considered an event. Subjects in whom mortality or hospitalization was of a non-cardiac etiology were treated as censored cases.

Patients lost to follow-up were considered to be anyone who was not tracked for one year and did not have an event; 56 patients were not tracked for one year and were not included in the final analysis.

Echocardiography. Standard M-mode and two-dimensional echocardiography and Doppler blood flow measurements were performed in agreement with the American Society of Echocardiography guidelines (21). Septal and posterior LV wall thicknesses were obtained from the parasternal long-axis view. The LV end-systolic and end-diastolic volumes were obtained from two-dimensional apical images. The LVEF was calculated from two-dimensional apical images according to the Simpson method. The LV mass was calculated according to the formula proposed by Devereux et al. (22). Pulsed-wave Doppler echocardiography was used to assess mitral peak early (E) and late (A) wave flow velocity and E-wave deceleration time. Isovolumic relaxation time was also determined.

Doppler mitral in-flow velocities were used to classify diastolic function according to the following classification: normal, rates of mitral E to A ratio >1 and E-wave deceleration time ≤220 ms; mild, rates of mitral E to A ratio <1 and E-wave deceleration time >220 m; moderate, rates of mitral E to A ratio 1 to 2 and E-wave deceleration time 150 to 200 ms; severe, rates of mitral E to A ratio >2 and E-wave deceleration time <150 ms (1,23,24).

CPET procedure and data collection. Symptom-limited CPET was performed in all patients after written informed consent had been obtained. All centers used individualized ramp protocols, and maximal tests were planned to obtain an exercise duration between 8 and 10 min. Centers in the U.S. used treadmills and the Italian center used a cycle ergometer. A potential prognostic bias derived by comparing different exercise modes can reasonably be excluded considering that in a previous study the comparison between these two modes of exercise led to the identical predictive cutoff value for both peak V_{O_2} and V_E/V_{CO_2} slope (25). Standard 12-lead electrocardiograms were obtained at rest, each minute during exercise, and for at least five minutes during the recovery phase; blood pressure was measured using a standard cuff sphygmomanometer. Minute ventilation (V_E, body temperature, ambient pressure, saturated with water), oxygen uptake (V_{O_2}, standard pressure and temperature, dry [STPD]), carbon dioxide output (V_{CO_2}, STPD) and other cardiopulmonary variables were acquired breath-by-breath, averaged over 30 s, and printed in rolling averages every 10 s. The V-slope method was used to measure the anaerobic threshold (26). Although different methods for calculating the V_E/V_{CO_2} slope have been proposed, we measured this variable by including all data points from the beginning to the end of

Table 1. Patient Demographic and Clinical Characteristics According to Three Different LVEF Cutoffs

	LVEF ≥40%		LVEF ≥45%		LVEF ≥50%	
	SHF	DHF	SHF	DHF	SHF	DHF
n	264	145	316	93	363	46
Age, yrs	56.5 ± 13.1	58.1 ± 13.0	56.8 ± 13.1	57.8 ± 13.2	57.0 ± 13.1	57.9 ± 13.0
Gender (men/women), %	80/20	85/15	82/18	81/19	82/18	83/17
Etiology (CAD, hypertensive, idiopathic)	146/50/68	78/62/5	178/60/78	46/44/3	200/75/88	24/20/2
LVEF, %	26.0 ± 7.9	46.1 ± 5.9*	28.4 ± 9.0	49.1 ± 5.1*	30.6 ± 10.2	53.0 ± 4.9*
CPET data						
Exercise time, s	540 ± 80	555 ± 60	545 ± 70	542 ± 64	560 ± 60	538 ± 80
Peak V_{O_2}, $ml \cdot min^{-1} \cdot kg^{-1}$	15.5 ± 5.2	17.9 ± 6.1*	15.8 ± 5.3	18.1 ± 6.3*	16.1 ± 5.5	18.4 ± 6.8*
V_E/V_{CO_2} slope	35.5 ± 8.8	30.5 ± 6.7*	34.7 ± 8.7	30.4 ± 6.6*	34.2 ± 8.5	30.2 ± 7.6†
RER	1.06 ± 0.15	1.06 ± 0.17	1.06 ± 0.15	1.05 ± 0.16	1.06 ± 0.16	1.05 ± 0.14
Peak heart rate, beats/min	131.0 ± 29.6	133.9 ± 24.3	130.4 ± 28.7	138.3 ± 25.0	131.5 ± 28.7	135.6 ± 26.1
Therapy distribution						
ACE inhibitors, %	75	70	73	68†	63	63
Beta-blockers, %	45	35†	43	34†	43	30†
Diuretics, %	62	41†	60	36*	58	28*
Digoxin, %	57	35†	55	30*	52	24*
Aspirin, %	40	30†	45	25*	50	20*
Statins, %	60	50†	66	44*	72	38*

*$p < 0.01$ vs. SHF; †$p < 0.05$ vs. SHF.

ACE = angiotensin-converting enzyme; CAD = coronary artery disease; CPET = cardiopulmonary exercise test; DHF = diastolic heart failure; LVEF = left ventricular ejection fraction; RER = respiratory exchange ratio; SHF = systolic heart failure; V_{O_2} = oxygen uptake; V_E/V_{CO_2} = ventilation to carbon dioxide output.

exercise, in agreement with what has recently been shown by our group (27) and others (28). We reasoned that this was the preferable method for preventing variability among laboratories.

Statistical analysis. Univariate Cox regression analysis was used to determine the prognostic ability of peak V_{O_2} and V_E/V_{CO_2} slope. Multivariate Cox regression analysis was then performed using a forward stepwise approach to assess the combined prognostic effects of these variables in predicting total mortality and hospitalization in all HF populations. Entry and removal p values for the multivariate analyses were set at 0.05 and 0.10, respectively.

Receiver operating characteristic (ROC) curves were constructed for the peak V_{O_2} and V_E/V_{CO_2} slope classification schemes for the mortality end points. A z test was used to compare peak $VO_2$and the V_E/V_{CO_2} slope prognostic power (29). Optimal threshold values (highest combination of sensitivity/specificity) were identified via ROC curve analysis. The threshold value was determined when the z test showed a significant difference in area under the ROC curve between peak V_{O_2} and V_E/V_{CO_2} slope. Cox regression analysis retained only that parameter. Two threshold values were determined when the z test showed that the area under the ROC curves between peak V_{O_2} and the V_E/V_{CO_2} slope were not significantly different and multivariate Cox regression analysis retained both parameters. Kaplan-Meier analyses and hazard ratio calculations were subsequently performed with the threshold values. The log-rank test was used to compare the equality of survival distributions in the Kaplan-Meier analyses.

Intergroup differences between clinical and exercise variables were compared using unpaired *t* test analysis. All data are reported as mean values ± standard deviation. Statistical tests with a p value <0.05 were considered to be significant. All tests were performed using SPSS for Windows version 11.0 (SPSS Inc., Chicago, Illinois).

RESULTS

Over the one-year tracking period, there were 23 deaths and 90 hospitalizations for cardiac reasons. Table 1 reports the clinical characteristics and CPET data of the study populations according to LVEF cutoffs. In all groups, SHF and DHF patients had similar age and gender distributions. A significantly lower distribution of diuretics, aspirin, statins, and digoxin occurred in DHF patients with a LVEF ≥45% and ≥50%.

Patients exercised above their anaerobic threshold and achieved a high peak respiratory exchange ratio (RER) (≥1.05 in all groups), suggesting that they developed significant metabolic acidosis and exercised close to maximal intensity. In all groups, patients with SHF had a significantly lower peak V_{O_2} and a significantly higher V_E/V_{CO_2} slope. Peak HR, exercise time, and RER were not significantly different between SHF and DHF across identified populations.

Table 2 summarizes the echo-derived data. In all groups, DHF patients presented with significantly smaller LV volumes and masses. However, the ratio LV mass/LV end-diastolic volume was significantly lower in SHF. The DHF patients, irrespective of LVEF, showed a significantly lower E/A ratio and prolonged deceleration time.

Univariate Cox regression analysis showed that both peak V_{O_2}, except for the LVEF ≥45% group, and the V_E/V_{CO_2} slope were significant predictors of combined mortality and cardiac-related hospitalization in SHF and DHF groups (Table 3). Multivariate Cox regression analysis (Table 4) showed that both peak V_{O_2} and V_E/V_{CO_2} slope were predictors of mortality in SHF groups.

Table 2. Echocardiographic Data According to the Three LVEF Cutoffs

	LVEF ≥40%		LVEF ≥45%		LVEF ≥50%	
	SHF	DHF	SHF	DHF	SHF	DHF
LVESV, ml	105 ± 58	95 ± 60*	98 ± 64	89 ± 58†	70 ± 62	50 ± 57†
LVEDV, ml	179 ± 60	145 ± 65*	160 ± 65	115 ± 65†	150 ± 70	85 ± 64†
LVM, g	255 ± 50	230 ± 70*	240 ± 73	216 ± 70†	220 ± 75	200 ± 50†
LVM/LVEDV, g/ml	1.44 ± 0.8	1.60 ± 0.8*	1.50 ± 0.7	1.90 ± 0.9*	1.47 ± 0.9	2.35 ± 1.0†
Mitral inflow pattern						
IVRT, ms	102 ± 26	110 ± 25	104 ± 30	104 ± 34	105 ± 25	95 ± 36*
E, mm/s	90 ± 25	65 ± 25†	85 ± 25	68 ± 28†	80 ± 24	75 ± 24†
A, mm/s	36 ± 28	85 ± 25†	42 ± 25	80 ± 26†	44 ± 32	77 ± 32†
E/A ratio	2.5 ± 0.30	0.76 ± 0.30†	2.0 ± 0.36	0.85 ± 0.28†	1.8 ± 0.4	0.97 ± 0.5†
DT, ms	140 ± 60	345 ± 70†	170 ± 75	320 ± 80†	180 ± 70	300 ± 90†

*$p < 0.01$ vs. SHF; †$p < 0.05$ vs. SHF.
A = peak mitral late velocity; DT = deceleration time; E = peak mitral early velocity; IVRT = isovolumic relaxation time; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; LVM = left ventricular mass; other abbreviations as in Table 1.

In contrast, in DHF patients V_E/VCO_2 slope outnumbered peak VO_2, remaining the only CPET predictor regardless of LVEF (residual chi-square = 9.9, p = 0.002 for LVEF ≥40%; residual chi-square = 8.6, p = 0.003 for LVEF ≥45%; and residual chi-square = 14.5, $p < 0.001$ for LVEF ≥50%). The ROC curve analysis results for the peak VO_2 and V_E/VCO_2 slope classifications are presented in Table 5. In all groups of SHF and DHF patients, the area under the ROC curve was greater for the V_E/VCO_2 slope than for peak VO_2. In DHF, the best V_E/VCO_2 cutoff identified was 32.6 (sensitivity of 74% and specificity of 52%) for LVEF ≥40%; 33.1 (sensitivity of 76% and specificity of 62%) for LVEF ≥45%; and 33.3 (sensitivity of 97% and specificity of 40%) for LVEF ≥50%.

Kaplan-Meier curves for the combined end point mortality and cardiac-related hospitalization using these V_E/VCO_2 slope cutoffs for both SHF and DHF are shown in Figures 1 through 3.

DISCUSSION

It is widely accepted that peak VO_2, and, more recently V_E/VCO_2 slope, are strong prognostic markers in HF populations with impaired LV function (6–12). Previous reports have, however, primarily focused on the prognostic applications of CEPT variables in SHF patients. Although the present results confirm that in SHF patients both peak VO_2 and V_E/VCO_2 slope retain a prognostic value, the new finding was that a steep V_E/VCO_2 slope, compared with peak VO_2, is a more powerful prognostic marker in patients with DHF. Thus, abnormalities in exercise ventilation that can be determined submaximally and reflect the constellation of central and peripheral factors that underlie exercise intolerance in HF powerfully predict outcomes in both SHF and DHF. Although a need for definitive standardization of HF with preserved systolic function or DHF has been repeatedly emphasized and considerable effort has been posed on it (17–19),

Table 3. Univariate Cox Regression Analyses for Peak VO_2 and V_E/VCO_2 Slope

	Events	Number of Events	Chi-Square	p Value
LVEF ≥40%				
SHF				
Peak VO_2 (</≥14.0 $ml \cdot min^{-1} \cdot kg^{-1}$ threshold)	Mortality/hospitalization	20/62	39.7	<0.001
V_E/VCO_2 slope (</≥35.9 threshold)	Mortality/hospitalization	20/62	48.3	<0.001
DHF				
Peak VO_2 (</≥14.2 $ml \cdot min^{-1} \cdot kg^{-1}$ threshold)	Mortality/hospitalization	3/28	4.3	0.04
V_E/VCO_2 slope (</≥32.6 threshold)	Mortality/hospitalization	3/28	9.9	0.002
LVEF ≥45%				
SHF				
Peak VO_2 (</≥14.1 $ml \cdot min^{-1} \cdot kg^{-1}$ threshold)	Mortality/hospitalization	21/71	42.2	<0.001
V_E/VCO_2 slope (</≥35.6 threshold)	Mortality/hospitalization	21/71	50.8	<0.001
DHF				
Peak VO_2 (</≥14.2 $ml \cdot min^{-1} \cdot kg^{-1}$ threshold)	Mortality/hospitalization	2/19	2.4	0.12
V_E/VCO_2 slope (</≥33.1 threshold)	Mortality/hospitalization	2/19	8.6	0.003
LVEF ≥50%				
SHF				
Peak VO_2 (</≥14.3 $ml \cdot min^{-1} \cdot kg^{-1}$ threshold)	Mortality/hospitalization	22/81	43.8	<0.001
V_E/VCO_2 slope (</≥34.4 threshold)	Mortality/hospitalization	22/81	48.4	<0.001
DHF				
Peak VO_2 (</≥10.6 $ml \cdot min^{-1} \cdot kg^{-1}$ threshold)	Mortality/hospitalization	1/9	10.4	0.001
V_E/VCO_2 slope (</≥33.3 threshold)	Mortality/hospitalization	1/9	14.5	<0.001

Abbreviations as in Table 1.

Table 4. Multivariate Cox Regression Analyses for Peak VO_2 and VE/VCO_2 Slope

		SHF			DHF		
Predictor Variable	Events	Number of Events	Chi-Square	p Value	Number of Events	Chi-Square	p Value
LVEF ≥40%							
Strongest predictor variable							
VE/VCO_2 slope	Mortality/hospitalization	20/62	48.3	<0.001	3/28	9.9	0.002
Added predicted value from second variable							
Peak VO_2	Mortality/hospitalization	20/62	17.4	<0.001	3/28	1.1	0.29
LVEF ≥45%							
Strongest predictor variable							
VE/VCO_2 slope	Mortality/hospitalization	21/71	50.8	<0.001	2/19	8.6	0.003
Added predicted value from second variable							
Peak VO_2	Mortality/hospitalization	21/71	16.9	0.001	2/19	1.1	0.29
LVEF ≥50%							
Strongest predictor variable							
VE/VCO_2 slope	Mortality/hospitalization	22/81	48.4	<0.001	1/9	14.5	<0.001
Added predicted value from second variable							
Peak VO_2	Mortality/hospitalization	22/81	20.5	<0.001	1/9	1.4	0.24

Abbreviations as in Table 1.

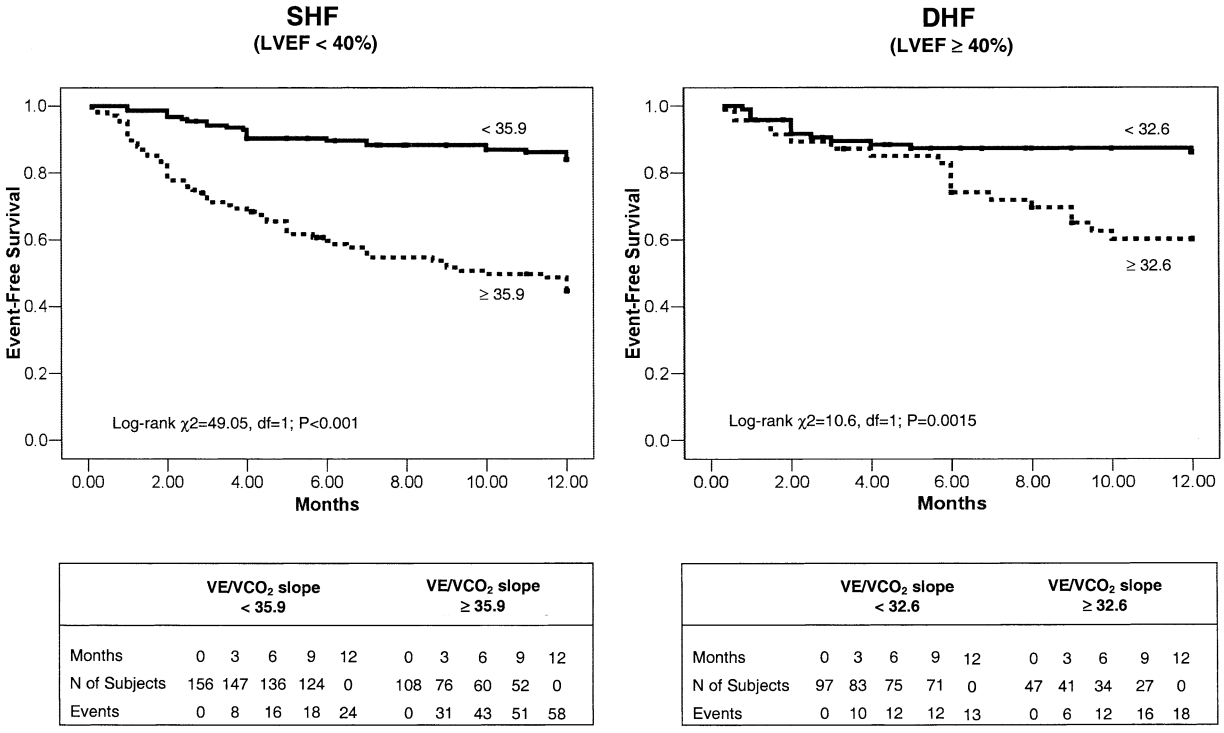
a precise and accepted definition is still under scrutiny. In previous observational studies, a preserved systolic function was defined on divergent LVEF cutoffs ranging from 40% to 50% (14–19). This obviously precludes a direct comparison between findings in different studies and may explain why most questions and clinical issues related to DHF remain to be answered. To circumvent this problem, we performed the analysis by grouping patients according to the three different LVEF cutoffs. Interestingly, in all groups categorized as DHF, VE/VCO_2 slope showed a similar prognostic power regardless of the LVEF cutoff considered. A potential additional strength of the present investigation stands on the use of a combined mortality/cardiac-related hospitalization end point.

Most studies examining the prognostic value of CPET have not used hospitalization as an end point. Given that HF is the primary hospital diagnosis-related group among Medicare patients, and considering that the one-year readmission rate of DHF is nearly identical to that for SHF and approaches 50% (30–32), analysis of measures predicting hospitalization in this population seems warranted.

Table 5. Receiving Operating Characteristics Curve Analyses for Combined End Point Mortality and Hospitalization

	Area Under the Curve	95% Confidence Interval	p Value	Optimal Prognostic Threshold Value
LVEF ≥ 40%				
SHF				
Peak VO_2	0.76	0.70–0.82	<0.001	14.0 (69% sensitivity/73% specificity)
VE/VCO_2 slope	0.81	0.76–0.86	<0.001	35.9 (73% sensitivity/71% specificity)
DHF				
Peak VO_2	0.66	0.55–0.76	0.001	14.2 (74% sensitivity/52% specificity)
VE/VCO_2 slope	0.69	0.59–0.79	0.008	32.6 (74% sensitivity/52% specificity)
LVEF ≥ 45%				
SHF				
Peak VO_2	0.76	0.70–0.81	<0.001	14.1 (70% sensitivity/71% specificity)
VE/VCO_2 slope	0.79	0.74–0.81	<0.001	35.6 (70% sensitivity/71% specificity)
DHF				
Peak VO_2	0.63	0.48–0.77	0.08	14.2 (75% sensitivity/43% specificity)
VE/VCO_2 slope	0.72	0.60–0.84	0.002	33.1 (76% sensitivity/62% specificity)
LVEF ≥ 50%				
SHF				
Peak VO_2	0.74	0.72–0.82	<0.001	34.4 (70% sensitivity/70% specificity)
VE/VCO_2 slope	0.77	0.69–0.80	<0.001	34.4 (70% sensitivity/70% specificity)
DHF				
Peak VO_2	0.61	0.62–0.98	0.03	10.6 (97% sensitivity/70% specificity)
VE/VCO_2 slope	0.80	0.39–0.83	0.005	33.3 (97% sensitivity/40% specificity)

Abbreviations as in Table 1.

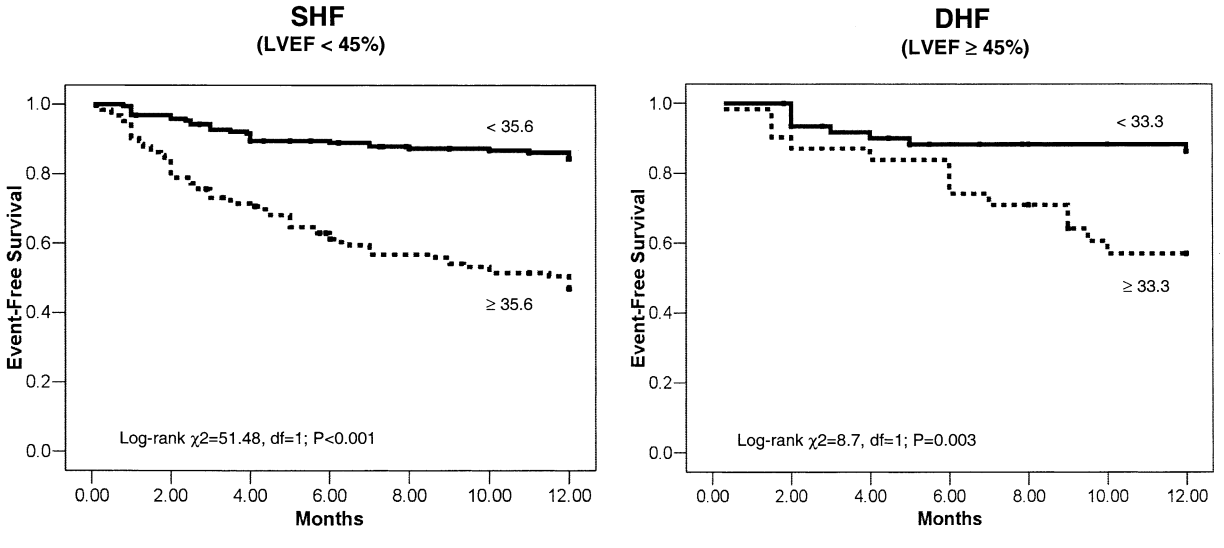


	VE/VCO₂ slope < 35.9					VE/VCO₂ slope ≥ 35.9				
Months	0	3	6	9	12	0	3	6	9	12
N of Subjects	156	147	136	124	0	108	76	60	52	0
Events	0	8	16	18	24	0	31	43	51	58

	VE/VCO₂ slope < 32.6					VE/VCO₂ slope ≥ 32.6				
Months	0	3	6	9	12	0	3	6	9	12
N of Subjects	97	83	75	71	0	47	41	34	27	0
Events	0	10	12	12	13	0	6	12	16	18

Figure 1. Kaplan-Meier survival curves according to VE/VCO_2 slope in SHF and DHF using a LVEF cutoff value of ≥40%. DHF = diastolic heart failure; LVEF = left ventricular ejection fraction; SHF = systolic heart failure; VE = ventilation; VO_2 = oxygen uptake.

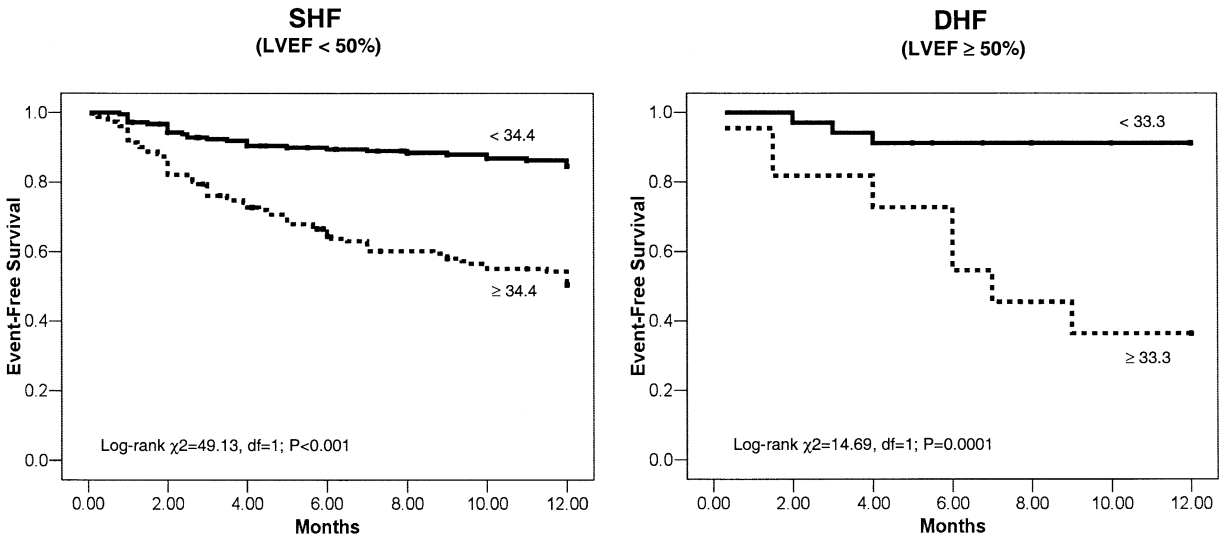
VE/VCO_2 slope versus peak VO_2: prognostic value. In a study by Ponikowski et al. (33), it was observed that a subgroup of patients with depressed LV function but normal peak VO_2 (≥18 ml · min^{-1} · kg^{-1}) and a VE/VCO_2 slope ≥34 had a significantly higher mortality rate than patients with a normal peak VO_2 and a VE/VCO_2 slope <34. This provocative study was the first to introduce the concept that ventilatory inefficiency during exercise predicts mortal-



	VE/VCO₂ slope < 35.6					VE/VCO₂ slope ≥ 35.6				
Months	0	3	6	9	12	0	3	6	9	12
N of Subjects	192	176	165	150	0	123	89	70	61	0
Events	0	14	21	24	29	0	33	47	55	63

	VE/VCO₂ slope < 33.3					VE/VCO₂ slope ≥ 33.3				
Months	0	3	6	9	12	0	3	6	9	12
N of Subjects	62	54	47	44	0	31	27	23	18	0
Events	0	5	7	7	8	0	4	8	11	13

Figure 2. Kaplan-Meier survival curves according to VE/VCO_2 slope in SHF and DHF using a LVEF cutoff value of ≥45%. Abbreviations as in Figure 1.



	VE/VCO_2 slope < 34.4					VE/VCO_2 slope ≥ 34.4				
Months	0	3	6	9	12	0	3	6	9	12
N of Subjects	212	191	79	165	0	151	114	92	72	0
Events	0	16	22	25	31	0	36	53	62	72

	VE/VCO_2 slope < 33.3					VE/VCO_2 slope ≥ 33.3				
Months	0	3	6	9	12	0	3	6	9	12
N of Subjects	34	32	28	26	0	11	8	6	4	0
Events	0	2	3	3	3	0	3	5	7	7

Figure 3. Kaplan-Meier survival curves according to VE/VCO_2 slope in SHF and DHF using a LVEF cutoff value of ≥50%. Abbreviations as in Figure 1.

ity in HF even in the presence of a normal peak VO_2. Our results confirm this observation and extend it to HF patients with preserved LVEF. This further challenges the belief that the greater the severity of the syndrome, the steeper the VE/VCO_2slope; an assumption that again has been generated by the analysis of prospective trials exclusively including patients with significant reduction in LVEF.

Interestingly, in all DHF groups the identified cutoffs for VE/VCO_2 slope were definitively similar to the cutoff of 34 that has been identified as a reference value in previous studies (6–12) for populations with depressed LV systolic function. Together, these observations suggest that an impairment in ventilatory efficiency should be considered a hallmark for the estimation of risk among patients with HF, and that these risk estimates are equally powerful among patients with reduced and preserved systolic function. As a parallel finding, we observed in all DHF patients that peak VO_2 was significantly higher whereas VE/VCO_2 slope was significantly lower in DHF compared with SHF, suggesting that there is a significant difference in functional capacity and physical performance between the two conditions. These findings, along with the lower mortality rate, suggest that despite the fact that DHF is a syndrome that is increasing in prevalence and that has a high morbidity, the natural history and clinical course are less severe than those for SHF (2,17).

CPET features of DHF. In a recent study characterizing exercise pathophysiological features of DHF, Kitzman et al. (4) reported that, among 50 patients with DHF, the peak exercise VE/VCO_2 ratio was similar to that observed in patients with SHF. Although average peak VO_2 was lower than that observed in our population, it was still significantly higher in comparison with that for patients with SHF. Differences between the results of Kitzman et al. (4) and our findings may be explained by considering that the VE/VCO_2 ratio does not necessarily parallel the slope of this relationship; identical ratios may occur with markedly different slopes. Another important difference is that the average age of patients was considerably higher than that in our population, which likely accounts for the differences in peak VO_2.

Study limitations. We did not investigate the pathophysiological mechanisms that lead to ventilatory inefficiency in patients with DHF. Specifically, we do not know the extent to which the increased VE/VCO_2 slope is secondary to uneven perfusion/ventilation matching, or whether it reflects muscle deconditioning with early metabolic acidosis or ergoreflex activation. This is an unanswered question that needs to be addressed in future studies, and has important implications for optimizing therapeutic strategies in diastolic HF. In addition, the total number of DHF patients was small. However, given the recognized lower mortality rate in these patients and considering our final combined end point, i.e., total mortality and hospitalization, the sample size seems adequate for drawing preliminary conclusions. At least in patients with SHF, beta-blocker distribution was suboptimal. The main reason is that, apart from patients who did not tolerate beta-blocker titration, some patients were already receiving digoxin, and beta-blocker titration to high effective doses was not tolerated.

Compared with other DHF populations, the female gender distribution in our study patients was quite low (12%) (4,34,35). This suggests that some caution may be warranted in the extrapolation of our findings to a predominantly female gender population of HF patients with preserved systolic function (4).

CONCLUSIONS

These results extend the clinical and prognostic applicability of CPET-derived variables to patients with DHF and preserved LVEF. An impaired ventilation rather than peak V_{O_2} holds clinical and prognostic impact in this population. Given the increasing burden of DHF, our findings may help to better characterize the natural history, treatment, and estimation of risk in DHF.

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