

Prognostic Usefulness of Dyspnea Versus Fatigue as Reason for Exercise Test Termination in Patients With Heart Failure

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Cardiopulmonary exercise testing (CPX) is an integral tool for assessing the clinical status and prognosis of patients with heart failure (HF). The present investigation examined differences in CPX variables and prognosis according to reason for test termination. One hundred eighty-three patients with HF (69% men, 31% women; mean age 53 ± 13 years, left ventricular ejection fraction at rest $24.3 \pm 9.9\%$) underwent CPX in which the minute ventilation/carbon dioxide production slope, peak oxygen consumption, and peak respiratory exchange ratio were determined. Subjects were tracked for cardiac-related events for 2 years after CPX. Dyspnea and fatigue (general fatigue/leg fatigue) were the primary reasons for test termination in 79 and 104 patients, respectively. Peak oxygen consumption (15.4 ± 5.7 vs 17.5 ± 5.9 ml $\text{O}_2 \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) was significantly lower, whereas minute ventilation/carbon dioxide production slope (38.5 ± 12.8 vs 33.9 ± 9.8) was significantly higher in the dyspnea subgroup ($p < 0.05$). There were 41 cardiac-related events during the 2-year tracking period. Patients with dyspnea were at significantly higher risk of adverse events (hazard ratio 2.1, 95% confidence interval 1.1 to 4.0, $p = 0.02$). In conclusion, these results indicate that patients with HF terminating an exercise test primarily because of dyspnea have an increased incidence of cardiac-related events and poorer CPX markers than those limited by fatigue. © 2008 Elsevier Inc. All rights reserved. (Am J Cardiol 2008;102:879–882)

In patients with heart failure (HF), cardiopulmonary exercise (CPX) tests are often terminated secondary to patient request, with fatigue and dyspnea the most commonly reported limiting factors. These are also the predominate symptoms that limit daily activities in the HF population. It was reported that apparently healthy patients who reported dyspnea as the reason for termination of an exercise test had significantly higher rates of cardiac and all-cause mortality compared with patients reporting other symptoms.¹ It was also reported that patients with and without known cardiac artery disease referred for exercise testing because of dyspnea were at increased risk of cardiac-related mortality.² Examination of differences in characteristics of CPX variables according to patient symptoms and the prognostic significance of this important subjective response in the HF population were lacking. The purpose of the present investigation was therefore to examine differences in CPX variables and prognosis according to reasons for patient-initiated termination of testing.

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Methods

This study was conducted by the LeBauer Cardiovascular Research Foundation, Greensboro, North Carolina. Data used in this analysis were captured as part of a HF CPX registry maintained by the LeBauer Cardiovascular Research Foundation. A total of 394 patients with chronic HF underwent routine testing from May 8, 2003, to June 19, 2007, at Duke University Medical Center (Durham, North Carolina) or Moses Cone Memorial Hospital (Greensboro, North Carolina). For this analysis, inclusion criteria consisted of a diagnosis of HF,³ evidence of left ventricular systolic dysfunction using 2-dimensional echocardiography obtained within 1 month of exercise testing, and patient-initiated test termination because of dyspnea or fatigue. Patients with a diagnosis of chronic obstructive pulmonary disease, those with oxygen desaturation (oxygen saturation measured using pulse oximetry $< 90\%$ using pulse-oximetry) during the test, technician-initiated test termination, and patients who cited other reasons for terminating the test as the primary reason for stopping (i.e., chest pain, lightheadedness/dizziness, and orthopedic pain) were excluded. A total of 183 patients met all inclusion criteria, with no exclusions, and were used in this analysis. All subjects completed a written informed consent, and institutional review board approval was obtained by the LeBauer Cardiovascular Research Foundation at the respective institutions.

Symptom-limited CPX was performed on all patients using a treadmill ($n = 153$) or lower-extremity ergometer ($n = 30$) staged protocols. The treadmill protocol was a modified Naughton protocol, and a 10-W/min protocol was

Table 1
Overall group characteristics and symptom subgroup comparisons

Variable	Overall Group (n = 183)	Fatigue (n = 104)	Dyspnea (n = 79)
Age (yrs)	53 ± 13	53 ± 13	53 ± 14
Body mass index (kg/m ²)	29.0 ± 6.3	28.9 ± 5.7	29.1 ± 7.0
Men/women	127 (69%)/56 (31%)	75 (72%)/29 (28%)	52 (66%)/27 (34%)
Left ventricular ejection fraction	24.3 ± 9.9%	24.5 ± 9.0%	24.1 ± 10.9%
History of smoking (yes/no)	74 (40%)/109 (60%)	41 (39%)/63 (61%)	33 (42%)/46 (58%)
New York Heart Association class			
I	19 (10%)	12 (12%)	7 (9%)
II	60 (33%)	45 (43%)*	15 (19%)
III	86 (47%)	40 (38%)	46 (58%)*
IV	18 (10%)	7 (7%)	11 (14%)
Cause (ischemic/nonischemic)	66 (36%)/117 (64%)	38 (37%)/66 (63%)	28 (35%)/51 (65%)
Prescribed angiotensin-converting enzyme inhibitor	138 (75%)	81 (78%)	57 (72%)
Prescribed diuretic	153 (84%)	83 (80%)	70 (89%)

* p < 0.05, fatigue versus dyspnea groups.

Table 2
Overall group pre-exercise spirometry and symptom subgroup comparisons

Variable	Overall Group (n = 183)	Fatigue (n = 104)	Dyspnea (n = 79)
Forced vital capacity (L)	3.25 ± 1.06	3.17 ± 1.00	3.36 ± 1.13
Predicted forced vital capacity (%)	74.9 ± 18.1%	74.3 ± 17.2%	75.7 ± 19.2
Forced expiratory volume in 1 second (L)	2.43 ± 0.83	2.44 ± 0.83	2.41 ± 0.88
Predicted forced expiratory volume in 1 second (%)	70.3 ± 20.3%	71.7 ± 19.5%	68.5 ± 21.1
Forced expiratory volume in 1 second/forced vital capacity	74.9 ± 11.4%	76.7 ± 10.0%*	72.6 ± 12.6%
Maximal voluntary ventilation	101 ± 37	104 ± 36	96 ± 38
Predicted maximal voluntary ventilation (%)	75.2 ± 22.8	77.9 ± 21.3%	71.7 ± 24.4%

* p < 0.05, fatigue versus dyspnea groups.

used for the lower-extremity ergometer. Previous studies have shown the prognostic thresholds of peak peak oxygen consumption ($\dot{V}O_2$) and minute ventilation/carbon dioxide production ($\dot{V}E/\dot{V}CO_2$) slope in patients with HF to be similar irrespective of mode of exercise.⁴ Although more patients in the fatigue group than the dyspnea group were tested on a lower-extremity ergometer (22 vs 7), this was not found to be a significant difference ($p > 0.05$). Therefore, lower-extremity ergometer tests were maintained in the analysis. Spirometry was performed before the exercise test in accordance with American Thoracic Society guidelines for spirometry,⁵ in which forced vital capacity, forced expiratory volume in 1 second, and maximal voluntary ventilation were recorded. Ventilatory expired gas analysis (as well as spirometry) was performed using a metabolic cart (Medgraphics CPX-D or ULTIMA PFX, Minneapolis, Minnesota; Parvo Medics TrueOne 2400, Sandy, Utah; or SensorMedics Vmax29, Yorba Linda, California). Before each test, the equipment was calibrated according to the manufacturer's recommendation. In addition, metabolic exercise testing equipment was routinely validated by exercising a healthy subject at a submaximal steady rate to verify that measured $\dot{V}O_2$ matched estimated $\dot{V}O_2$ from the workload.⁶ Standard 12-lead electrocardiograms were obtained at rest, each minute during exercise, and for ≥ 5 minutes during the recovery phase. Blood pressure was measured using a standard cuff sphygmomanometer at rest, during exercise, and for ≥ 5 minutes during recovery. $\dot{V}E$,

body temperature, pressure, saturated (BTPS), $\dot{V}O_2$, standard temperature, pressure, dry (STPD), $\dot{V}CO_2$ (STPD), and other cardiopulmonary variables were acquired breath by breath and averaged over 15-second intervals. Peak $\dot{V}O_2$ and peak respiratory exchange ratio were expressed as the highest averaged samples obtained during the last minute of the exercise test. $\dot{V}E$ and $\dot{V}CO_2$ values, acquired from the initiation of exercise to peak, were input into spreadsheet software (Microsoft Excel; Microsoft Corp., Bellevue, Washington) to calculate the $\dot{V}E/\dot{V}CO_2$ slope using least-squares linear regression ($y = mx + b$, $m = \text{slope}$).

A nonleading question, such as "What was the main reason you felt like you needed to stop the exercise?," was asked of patients to identify the primary exercise-limiting symptom immediately after testing. Responses such as "I was tired," "My legs were tired," and "My legs were feeling weak" were defined as fatigue or leg fatigue. Responses such as "I could not catch my breath," "I could not breathe anymore," and "I had difficulty breathing" were defined as dyspnea. Although these are examples of responses patients have given, it was up to the technicians (all with master's degrees and American College of Sports Medicine certification; 2 exercise specialists and 1 registered clinical exercise physiologist) to interpret the response.

Subjects were followed up for time to first cardiac-related event for a maximum of 2 years after CPX using hospital and outpatient medical chart review. Subjects were seen by the HF programs at each institution and followed up

Table 3
Overall group exercise and symptom subgroup comparisons

Variable	Overall Group (n = 183)	Fatigue (n = 104)	Dyspnea (n = 79)
Heart rate at rest (beats/min)*	74 ± 13	72 ± 12	76 ± 14*
Peak heart rate (beats/min)	126 ± 24	128 ± 25	125 ± 23
Systolic blood pressure at rest (mm Hg)	113 ± 22	113 ± 23	112 ± 21
Peak systolic blood pressure (mm Hg)*	143 ± 34	148 ± 34*	136 ± 33
Diastolic blood pressure at rest (mm Hg)	70 ± 13	70 ± 13	69 ± 13
Peak diastolic blood pressure (mm Hg)	74 ± 18	75 ± 15	73 ± 21
Peak VO ₂ (ml O ₂ · kg ⁻¹ · min ⁻¹)*	16.6 ± 5.9	17.5 ± 5.9*	15.4 ± 5.7
Ventilatory efficiency slope*	35.9 ± 11.4	33.9 ± 9.8	38.5 ± 12.8*
Peak respiratory exchange ratio	1.13 ± 0.11	1.13 ± 0.10	1.11 ± 0.11
Peak ventilation (L/min)*	60.4 ± 21.2	61.9 ± 20.9*	58.5 ± 18.0
Peak ventilation/maximal voluntary ventilation*	61.2 ± 17.0%	58.3 ± 15.4%	65.1 ± 18.3%*
Oxygen consumption at ventilatory threshold (ml O ₂ · kg ⁻¹ · min ⁻¹)	11.7 ± 3.7	11.8 ± 3.5	11.6 ± 3.9

* p < 0.05, fatigue versus dyspnea groups.

by the LeBauer Cardiovascular Research Foundation, providing for the high likelihood that all events were captured. Cardiac-related hospitalization, heart transplantation, left ventricular assist device implantation, and cardiac-related death were considered events. Any hospitalization or death with a cardiac-related discharge diagnosis was considered an event. Clinicians conducting the CPX were not involved in decisions regarding hospitalization, cause of death, heart transplantation, or left ventricular assist device implantation.

Subjects were divided into exercise symptom subgroups (dyspnea or fatigue). All continuous data were reported as mean ± SD, and categorical data, as percentage. Unpaired *t* testing was used to assess differences in key continuous variables, whereas chi-square analysis assessed differences in categorical variables between the fatigue and dyspnea subgroups. Kaplan-Meier analysis assessed survival characteristics of the fatigue and dyspnea subgroups. Log-rank test was used to determine statistical significance for the Kaplan-Meier analysis. Univariate Cox regression analysis was used to assess the prognostic value of fatigue versus dyspnea as the primary symptom limiting exercise in the overall cohort. Statistical difference with *p* < 0.05 was considered significant.

Results

Seventy-nine subjects reported dyspnea as their primary symptom at peak exercise, whereas the remaining 104 reported fatigue. Mean values and percentages of key baseline characteristics, pre-exercise spirometry, and CPX variables for the overall group, as well as the dyspnea and fatigue subgroups, are listed in Tables 1, 2, and 3. New York Heart Association class was significantly higher in the dyspnea subgroup. Spirometry showed a significantly lower ratio of forced expiratory volume in 1 second to forced vital capacity in the dyspnea subgroup. With respect to CPX data, peak VO₂ and systolic blood pressure were significantly higher, whereas VE/VCO₂ slope and breathing reserve (ratio of VE/maximal voluntary ventilation) were significantly lower in the fatigue subgroup. Importantly, peak respiratory exchange ratio, an objective indicator of subject effort, was not significantly different between groups.

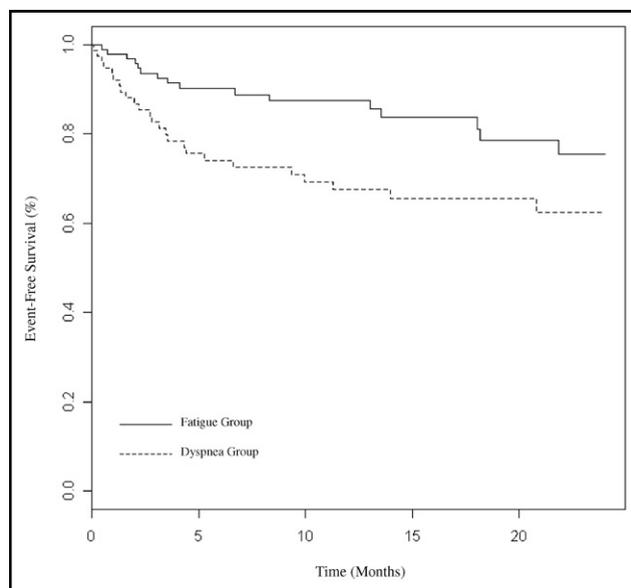


Figure 1. Kaplan-Meier analysis for 2-year cardiac-related events according to reason for exercise cessation. Fatigue group, 84.6% event-free survival (16 events in 104 patients); dyspnea group, 68.4% event-free survival (25 events in 79 patients). Log-rank = 5.7, *p* = 0.02.

There were 41 cardiac-related events (31 hospitalizations, 9 heart transplantations, and 1 death) during the 2-year tracking period (annual event rate 18.4%). Univariate Cox regression analysis showed that subjects who reported dyspnea as their primary symptom limiting exercise had a significantly higher risk of cardiac-related events (hazard ratio 2.1, 95% confidence interval 1.1 to 4.0, *p* = 0.02). Kaplan-Meier analysis results are shown in Figure 1. Differences in event-free survival were significant between the dyspnea and fatigue subgroups, with a higher event rate in the dyspnea group.

Discussion

Despite similar resting ejection fraction and medication prescribed between the 2 symptom subgroups, we observed

that subjects reporting dyspnea as the reason for terminating exercise had a higher New York Heart Association class, lower peak VO_2 , and higher VE/VCO_2 slope. Thus, baseline characteristics and exercise responses suggest a higher severity of HF in patients who are limited by dyspnea. Also, pre-exercise spirometry showed a lower ratio of forced expiratory volume in 1 second to forced vital capacity.

Bodegard et al² studied 2,014 apparently healthy men using exercise stress testing without gas exchange, but recorded the reason for exercise test termination. After following up these patients for 26 years, it was found that subjects stopping because of what they termed impaired breathing were at 1.9-fold increased risk of dying of coronary heart disease, 1.6-fold increased risk of dying of any cause, and 3.5-fold increased risk of dying of pulmonary disease compared with those reporting lower-leg fatigue. However, Abidov et al¹ evaluated 17,991 patients (those with and without known coronary artery disease) referred for cardiac stress testing for dyspnea and compared them with patients with chest pain (anginal and nonanginal). After almost 3 years of follow-up, it was found that patients presenting with dyspnea were at about 2.5-fold increased risk of death from a coronary cause. Exercise test results from the present evaluation were consistent with previous reports, and these results highlighted the idea that subjective variables reported during the exercise test were useful in risk stratification in patients with HF and low functional capacity.

We did not attempt to determine the mechanism for dyspnea. Our data showed differences in lung function between the 2 groups. However, previous reports did not show an association between these spirometry measures and HF severity.⁷⁻¹⁰ These reports also did not differentiate patients based on the reason for exercise test termination. However, Meyer et al⁹ showed respiratory muscle dysfunction (reduced maximal inspiratory pressure) in patients with HF, which correlated with peak VO_2 and was an independent prognostic marker. Also, alteration in ventilatory pattern or strategy (tidal volume-respiratory rate relation and prolonged inspiratory time to total breath time ratio) have been noted with the onset of dyspnea in patients with HF.^{10,11} The appearance of rapid and shallow ventilation, respiratory muscle dysfunction, and the accompanying sensation of dyspnea may be a result of myopathy in the diaphragm or possibly subclinical pulmonary edema. Unfortunately, variables such as tidal volume, respiratory rate, and breath time were not captured in this registry. Therefore, we could not confirm this occurrence in our cohort. Our group and others previously reported a strong association between higher VE/VCO_2 slope and higher rate of cardiac events.¹²⁻¹⁵ Although these reports did not differentiate between patients stopping because of dyspnea or fatigue, the present data showed an association between higher VE/VCO_2 slope, impaired peak VO_2 , increased occurrence of dyspnea, and higher event rates. The report of dyspnea may suggest later disease, more severe disease, or more severe deconditioning. Further research is needed to elucidate the relation between respiratory muscle dysfunction, ventilatory strategy, VE/VCO_2 slope, and dyspnea.

There were several limitations to this study. First, groupings were based on subjective responses recorded into a

registry database that were dependent on the interpretation of the patient of the question asked and the interpretation of the technician of the response by the patient. Future research should attempt to define these more clearly. Also, our sample was small, and future investigations in larger cohorts are needed to confirm our findings. Furthermore, the lack of specific respiratory data (tidal volume, respiratory rate, and breath time) did not allow us to confirm what others found in regard to these variables. Another limitation was that the overall younger age of our cohort may limit the use of these findings to older patients. Last, the relatively small number of women and patients with class IV HF may limit the application of the findings to these particular patient groups.

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