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Comparison of the prognostic value of cardiopulmonary exercise testing between male and female patients with heart failure

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Abstract

Background: Cardiopulmonary exercise testing (CPX) clearly holds prognostic value in the heart failure (HF) population. Studies investigating the prognostic value of CPX in individuals with HF have consistently examined predominantly male groups. The purpose of the present study was to examine the prognostic value of CPX in a female HF group.
Methods: Seventy-five female and 337 male subjects diagnosed with HF participated in this study. The ability of peak oxygen consumption (VO_2) and the minute ventilation/carbon dioxide production (VE/VCO_2) slope to predict cardiac-related events were assessed.
Results: In the year following CPX, the female group suffered 26 cardiac-related events (8 deaths/18 hospitalizations), while the male group suffered 89 cardiac-related events (20 deaths/69 hospitalizations). The hazard ratios for peak VO_2 and the VE/VCO_2 slope were 4.0 (95% confidence interval: 2.6–6.1, $p<0.001$) and 4.2 (95% confidence interval: 2.7–6.6, $p<0.001$) in the male group and 3.8 (95% confidence interval: 1.7–8.5, $p<0.001$) and 4.3 (95% confidence interval: 1.8–9.8, $p<0.001$) in the female group. In both the male and female groups, Cox multivariate analysis revealed VE/VCO_2 slope was the strongest predictor of cardiac-related events while peak VO_2 added significant predictive value and was retained in the regression.
Conclusion: The results of the present study indicate that the prognostic value of peak VO_2 and the VE/VCO_2 slope are similar in men and women diagnosed with HF. In both men and women, the prognostic power of the VE/VCO_2 slope is greater than that of peak VO_2.

Keywords: Ventilatory expired gas; Hospitalization; Mortality; Gender

1. Background

The body of evidence demonstrating the prognostic significance of cardiopulmonary exercise testing (CPX) in heart failure (HF) is rather robust [1–4]. As a result of this body of evidence, clinical utilization of CPX in the assessment of patients with HF is strongly endorsed [5,6]. Peak oxygen consumption (VO_2) and the relationship between minute ventilation and carbon dioxide (VE/VCO_2) are the most commonly assessed variables obtained from CPX. Both variables have demonstrated strong prognostic value [1,2,7,8] although the VE/VCO_2 relationship, commonly expressed as a slope, appears to be the superior prognostic marker. Furthermore, prognostic threshold values for peak VO_2 and the VE/VCO_2 slope have been proposed although there remains a lack of consensus in terms of defining a singular optimal threshold value for either variable [1,2,7,9,10].

Studies investigating the prognostic value of CPX in individuals with HF have consistently examined predominantly male groups. Utilizing predominantly male groups in HF research is not consistent with the reported incidence and prevalence of HF, which appears to be evenly distributed between males and females [11]. Given the gender disparity between groups assessed in research studies and the population seen in clinical practice, questions

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regarding the prognostic value of CPX in females diagnosed with HF remain.

The purpose of the present study was to: (1) compare key baseline and CPX values between males and females diagnosed with compensated HF; (2) assess the independent and combined prognostic value of peak VO_2 and the VE/VCO_2 slope in male and female subjects; and (3) assess the optimal prognostic threshold values for peak VO_2 and the VE/VCO_2 slope in male and female subjects.

2. Materials and methods

This was a multicenter retrospective analysis consisting of HF patients from the cardiopulmonary laboratories at San Paolo Hospital, Milan, Italy, Virginia Commonwealth University, Richmond, Virginia, USA and the VA Palo Alto Health Care System and Stanford University, Palo Alto, California, USA. A total of 412 consecutive patients with chronic HF were studied during a progressively increasing cycle ergometer ($n=135$, Italy) or treadmill exercise tests ($n=277$, USA). Previous work by our group has demonstrated optimal peak VO_2 and VE/VCO_2 slope prognostic threshold values were similar irrespective of mode of exercise in patients with HF [12]. We therefore did not create subgroups based upon mode of CPX. Exercise tests were conducted between 3/18/93 and 10/18/04. Seventy-five subjects were female, while the remaining 337 were male. All patients were between New York Heart Association (NYHA) functional classes I and III. Patients with significant obstructive lung disease or who were unable to perform a maximal exercise test were excluded from the study. All subjects completed a written informed consent and institutional review board approval was obtained at each institution. Baseline subject characteristics are listed in Table 1.

Table 1
Subject characteristics

	Males	Females
Number of subjects	337	75
Age (years)	57.5±13.2	55.0±12.3
Left ventricular ejection fraction (%)[a]	33.2%±11.9	32.9%±13.1
Mean NYHA class	2.2 (±0.65)	2.3 (±0.80)
Etiology (ischemic/non-ischemic)	187 (55%)/150 (45%)	49 (52%)/36 (48%)
Resting heart rate (beats/min)	80.4 (±16.9)	82.3 (±15.4)
Body mass index (kg/m^2)	28.1 (±5.4)	26.9 (±6.5)
ACE inhibitor (number of subjects and percentage)	241 (72%)	55 (73%)
Cardiac glycoside (number of subjects and percentage)	159 (47%)	44 (59%)
Diuretic (number of subjects and percentage)	177 (53%)	47 (63%)
Beta-blocker (number of subjects and percentage)	141 (42%)	29 (39%)

[a] Left ventricular ejection fraction was determined by echocardiography.

2.1. Equipment calibration

Ventilatory expired gas analysis was performed using a metabolic cart at all three centers (Medgraphics CPX-D, Minneapolis, MN or Sensormedics Vmax29, Yorba Linda, CA). The oxygen and carbon dioxide sensors were calibrated using gases with known oxygen, nitrogen and carbon dioxide concentrations prior to each test. The flow sensor was also calibrated before each test using a 3-l syringe.

2.2. CPX procedure and data collection

Symptom-limited CPX was performed in all patients using conservative treadmill [13] or cycle ergometry [14] ramping protocols. Standard 12-lead electrocardiograms were obtained at rest, each minute during exercise and for at least 5 min during the recovery phase; blood pressure was measured using a standard cuff sphygmomanometer. Minute ventilation (VE, BTPS), oxygen uptake (VO_2, STPD), carbon dioxide output (VCO_2, STPD) and other cardiopulmonary variables were acquired breath-by-breath, averaged over 30 s and printed in rolling averages every 10 s. Peak VO_2 and peak respiratory exchange ratio (RER) were expressed as the highest averaged samples obtained during the last 30 s of the exercise test. Subjects achieving an RER ≥ 1.00 were considered to have put forth a good effort. Using the rolling averages described above, VE and VCO_2 data, acquired from the initiation of exercise to peak, were input into spreadsheet software (Microsoft Excel, Microsoft Corp., Bellevue, WA) to calculate the VE/VCO_2 slope via least squares linear regression. Previous work by our group has shown this method of calculating the VE/VCO_2 slope to be prognostically optimal [15].

2.3. Endpoints

Subjects were followed for cardiac-related events (mortality or hospitalization) 1 year following CPX via medical chart review. Cardiac-related mortality was defined as death directly resulting from failure of the cardiac system. The most common causes of mortality, as per discharge diagnosis, were sudden cardiac death, myocardial infarction and HF. Cardiac-related hospitalization was defined as a hospital admission directly resulting from cardiac dysfunction requiring in-patient care. Any death or hospital admission with a cardiac-related discharge diagnosis, confirmed by diagnostic tests or autopsy, was considered an event. The most common causes of hospitalization were decompensated HF and coronary artery disease. Subjects in whom mortality or hospitalization was of a non-cardiac etiology were treated as censored cases.

2.4. Statistical analysis

Unpaired *t*-testing was used to compare differences in age, left ventricular ejection fraction (LVEF), peak RER,

Table 2
Cardiopulmonary exercise test variables

	Males	Females	p-value
Maximal heart rate (beats/min)	131.9 (±33.5)	133.5 (±25.9)	0.70
Peak VO_2 (ml O_2 kg^{-1} min^{-1})	17.1 (±5.7)	12.8 (±3.9)	<0.001
Peak RER	1.07 (±0.16)	1.02 (±0.12)	0.005
VE/VCO_2 slope	33.0 (±8.0)	37.3 (±9.3)	<0.001

peak VO_2 and the VE/VCO_2 slope between the male and female HF groups. The Man–Whitney U-test was used to assess differences in NYHA Classification between male and female HF groups.

Receiver operating characteristic (ROC) curves were constructed for peak VO_2 and VE/VCO_2 slope classification schemes for the male and female HF groups. Optimal threshold values (highest combination of sensitivity/specificity) were identified for the 1-year endpoints via ROC curve analysis and used in the subsequent Kaplan–Meier, univariate and multivariate Cox regression analyses.

Univariate Cox regression analysis assessed the ability of peak VO_2 and the VE/VCO_2 slope to predict 1-year cardiac-related events and to derive a hazard ratio for both variables. Multivariate Cox regression analysis (forward stepwise method), using peak VO_2 and VE/VCO_2 slope, was used to assess the combined effect of these variables in predicting 1-year cardiac-related events in males and females. Entry and removal p-values for the multivariate analyses were set at 0.05 and 0.10, respectively. Kaplan–Meier analysis was used to assess differences in cardiac-related events using variables retained in the multivariate Cox regression analysis in both the male and female groups. Kaplan–Meier analysis was also used to assess differences in event rate between the male and female HF groups. The log-rank test was used to determine if the difference in event-free survival was significant between subjects falling into different CPX derived categories for both males and females.

All data are reported as mean values ± standard deviation (S.D.). Statistical tests with a p-value <0.05 were considered significant.

3. Results

Results from Table 1 indicate age, body mass index, resting heart rate, NYHA classification and LVEF were not significantly different between the male and female groups. HF etiology and pharmacologic regimens were likewise similar between groups. Comparison of peak VO_2, peak RER and VE/VCO_2 slope between the male and female groups are listed in Table 2. Peak VO_2 and peak RER were significantly higher while VE/VCO_2 slope was significantly lower in the male group. Thirty-four females and 107 males had a peak RER < 1.00.

In the year following CPX, the female group suffered 26 cardiac-related events (8 deaths/18 hospitalizations), while the male group suffered 89 cardiac-related events (20 deaths/69 hospitalizations). This equated to 35% and 24% event rates in the female and male groups over the 1-year tracking period, respectively. Kaplan–Meier analy-

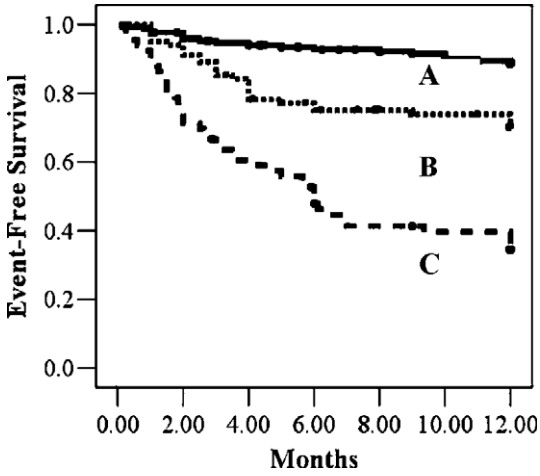

Fig. 1. Kaplan–Meier analysis for 1-year cardiac-related events in the male group using resting peak VO_2 threshold of ≤/>14.2 ml O_2 kg^{-1} min^{-1} and VE/VCO_2 slope threshold of </≥34.2.

Group	Characteristic	Subjects meeting criteria	Events	Percent event-free
A	Peak VO_2 > 14.2 ml O_2 kg^{-1} min^{-1} and VE/VCO_2 slope <34.2	170	18	89.1%
B	Peak VO_2 ≤ 14.2 ml O_2 kg^{-1} min^{-1} or VE/VCO_2 slope ≥24.3	101	29	71.3%
C	Peak VO_2 ≤ 14.2 ml O_2 kg^{-1} min^{-1} and VE/VCO_2 slope ≥34.2	66	42	36.4%

Log rank = 83.2, p < 0.0001
• = censored cases

Table 3
Receiver operating characteristic curve analysis

	Area under ROC curve	p-value	Optimal threshold value	Sensitivity	Specificity
Female group					
VE/VCO_2 slope	0.79	<0.001	36.1	74%	69%
Peak VO_2	0.75	<0.001	11.8 ml O_2 kg^{-1} min^{-1}	76%	69%
Male group					
VE/VCO_2 slope	0.78	<0.001	34.2	74%	65%
Peak VO_2	0.73	<0.001	14.2 ml O_2 kg^{-1} min^{-1}	77%	61%

sis revealed the event rate between the male and female HF groups was not statistically significant (log-rank: 0.97, $p=0.32$). ROC curve analysis results are listed in Table 3.

The peak VO_2 and VE/VCO_2 slope classification schemes were significant predictors of events in both the female and male groups. In addition, area under the ROC curve was comparable between genders. Optimal threshold values were, however, different between groups, with the VE/VCO_2 slope threshold being higher and the peak VO_2 threshold being lower in females compared to males (Table 3).

Peak VO_2 and VE/VCO_2 slope were both significant univariate predictors of cardiac-related events in the male and female HF groups. The hazard ratios for peak VO_2 and VE/VCO_2 slope in the male group were 4.0 (95% confidence interval: 2.6–6.1, $p<0.001$) and 4.2 (95% confidence interval: 2.7–6.6, $p<0.001$), respectively. The hazard ratios for peak VO_2 and VE/VCO_2 slope in females were 3.8 (95% confidence interval: 1.7–8.5, $p<0.001$) and 4.3 (95% confidence interval: 1.8–9.8, $p<0.001$), respectively. In the male group, Cox multivariate analysis revealed that the VE/VCO_2 slope was the strongest predictor of cardiac-related events (chi-square: 48.9, $p<0.001$), while peak VO_2 added significant predictive value and was retained in the regression (residual chi-square: 22.2, $p<0.001$). Likewise, in the female group, Cox multivariate analysis revealed that the VE/VCO_2 slope was the strongest predictor of cardiac-related events (chi-square: 13.6, $p<0.001$), while peak VO_2 again added significant predictive value and was retained in the regression (residual chi-square: 6.3, $p=0.01$).

Kaplan–Meier analysis results are illustrated in Figs. 1 and 2. Using the threshold values defined by ROC curve analysis produced a significant separation between individuals who were event-free and those experiencing a cardiac-related event within 1 year of the CPX in both the male and female groups. Those individuals with preferred values, as defined by ROC curve analysis, for both peak VO_2 and the VE/VCO_2 slope had the most favorable prognosis. Individuals with either an abnormal peak VO_2 or an abnormal VE/VCO_2 slope value demonstrated an intermediate prognosis, while individuals possessing abnormal values for both variables demonstrated the least favorable prognosis in both the males and females.

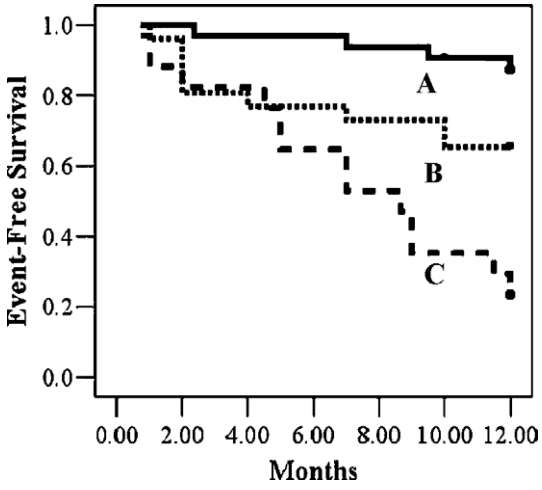

Fig. 2. Kaplan–Meier analysis for 1-year cardiac-related events in the female group using resting peak VO_2 threshold of ≤/>11.8 ml O_2 kg^{-1} min^{-1} and VE/VCO_2 slope threshold of </≥36.1

Group	Characteristic	Subjects meeting criteria	Events	Percent event-free
A	Peak VO_2 > 11.8 ml O_2 kg^{-1} min^{-1} and VE/VCO_2 slope <36.1	32	4	87.5%
B	Peak VO_2 ≤ 11.8 ml O_2 kg^{-1} min^{-1} or VE/VCO_2 slope ≥36.1	26	9	65.4%
C	Peak VO_2 ≤ 11.8 ml O_2 kg^{-1} min^{-1} and VE/VCO_2 slope ≥36.1	17	13	23.5%

Log rank=22.7, $p<0.0001$
•=censored cases

4. Discussion

Baseline male and female characteristics in the present study were similar with respect to age, LVEF, HF etiology and pharmacology. Key CPX variables were however, significantly different. Peak RER and peak VO_2 and were significantly higher, while the VE/VCO_2 slope was significantly lower in the male group. Previous research by our group has indicated that peak VO_2 and the VE/VCO_2 slope maintain prognostic value even when RER is low [16]. We therefore did not feel separation of subjects based upon peak RER was necessary. Although not previously demonstrated in subjects with HF, the significant difference in peak VO_2 between male and female subjects in our cohort may not prove to be surprising given a similar trend existed in apparently healthy individuals [17]. A gender-based difference in VE/VCO_2 slope among patients with HF, as reported in the present study, may however prove to be more intriguing. An elevated VE/VCO_2 slope in HF has been significantly correlated with worsening cardiac function [18,19], impaired matching of pulmonary ventilation and perfusion [20,21], an abnormal muscle ergoreceptor response [22] and abnormal chemosensitivity [23]. Patients studied in these previous investigations were either all-male or predominantly male. While it is likely that comparable physiologic mechanisms account for an elevated VE/VCO_2 slope in females with HF, the pattern of these relationships may differ compared to males with HF. Further research is required to examine the relationship between the VE/VCO_2 slope and cardiac function, ventilation to perfusion matching, ergoreceptor activity and chemosensitivity in the female HF population.

We are unaware of any previous investigation examining the influence of gender on the prognostic value of CPX in

HF. Consistent with numerous previous investigations [2,4,7,8], the major CPX variables (peak VO_2 and VE/VCO_2 slope) were significant predictors of outcomes in our HF cohort. In addition, several prognostic characteristics of these variables were similar for male and female subjects diagnosed with HF. Specifically, the area under the ROC curve for both peak VO_2 and the VE/VCO_2 slope were very similar between males and females, as were their respective hazard ratios. Second, the VE/VCO_2 slope was the superior predictor of risk, while peak VO_2 added significant prognostic value in both males and females. Third, using the optimal peak VO_2 and VE/VCO_2 slope threshold values, Kaplan–Meier analysis revealed similar event rates for subjects demonstrating favorable responses for both variables, one unfavorable and one favorable response, and no favorable responses between the male and female groups. Conversely, the optimal prognostic threshold values for peak VO_2 and the VE/VCO_2 slope were different between males and females, with the peak VO_2 threshold being higher and the VE/VCO_2 slope threshold being lower in the males. Again, most previous investigations recommending prognostic thresholds for peak VO_2 and the VE/VCO_2 slope have derived these values from predominantly males HF groups. The results of the present study suggest that, while prognostic characteristics may be similar between males and females with HF, separate gender-based prognostic threshold values may be appropriate when clinically applying CPX data.

Individuals with HF can shift from a stable to an uncompensated clinical status (or vice versa) rather abruptly. Limiting the post-CPX tracking period to 1 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 VE/VCO_2 slope and peak VO_2 in subjects with HF [24]. That analysis indicated that prognostic sensitivity modestly rose while specificity dramatically fell for both CPX variables greater than 1-year post-exercise testing. A 1-year tracking period may therefore strike an appropriate balance between avoiding outdated information and the economic constraints of multiple exercise tests.

Additionally, most research examining the prognostic value of CPX data do not use hospitalization as an endpoint. Given that HF is the primary hospital diagnostic-related group among Medicare patients [25], analysis of measures predicting hospitalization in this population seems warranted. The ability of peak VO_2 and the VE/VCO_2 slope to effectively predict hospitalization may help identify high-risk patients and provide appropriate interventions on an outpatient basis thereby preventing nonfatal adverse events (hospitalization) and reduce health care costs.

The relatively small size of the female group in the present study must be considered a limitation. Thus, additional research is required to support our findings. In addition, the small female group did not allow us to examine the influence of β-blockade use on the prognostic characteristics of peak VO_2 and the VE/VCO_2 slope. Several recent investigations have demonstrated peak VO_2 remains a strong predictor of outcomes in patients with HF receiving a β-blocking agent, although the optimal prognostic threshold value may be altered [26,27]. The influence of β-blockade use on the prognostic characteristics of the VE/VCO_2 slope has not been investigated. Future research should be directed toward examining the influence of β-blockade on the prognostic value of CPX in larger samples of females.

In conclusion, CPX continues to be an important clinical assessment in patients with compensated HF. The body of research establishing the prognostic importance of CPX has done so in predominantly male HF groups. The results of the present study indicate the prognostic value of CPX may be equally strong in females with HF, although optimal prognostic thresholds may differ compared to males. Given the incidence and prevalence of HF in females [11], future research in this area is warranted.

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