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Scientific Research

Prognostic Value of Cardiopulmonary Exercise Test in Elderly Women with Heart Failure and Reduced or Preserved Ejection Fraction

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Abstract

The prognostic role of cardiopulmonary exercise test (CPET) in elderly women with chronic heart failure (HF) has not yet been clarified. We assessed the incremental value of CPET variables for risk stratification in female HF patients with preserved or reduced left ventricular ejection fraction (LVEF). We prospectively followed up 131 female HF outpatients aged 72 [interquartile range 62 - 77] years after a symptom limited CPET. 34% had ischemic heart disease and 14% permanent atrial fibrillation, 24% were in NYHA class III. LVEF was 50% [interquartile range 36 - 62], peak oxygen consumption was 11.3 [interquartile range 9.2 - 13.5] ml/kg/min; the slope of the regression line relating ventilation to CO_2 output was 33.9 [interquartile range 30.3 - 44.9]; 40% of patients showed exercise oscillatory breathing during CPET. During a median follow-up of 18 months [interquartile range 8 - 54], overall 39 patients (29.7%) met the combined end-point of cardiovascular mortality or HF admission using a time-to-first event approach. Moderate to severe mitral regurgitation, slope, exercise oscillatory breathing were independently associated to cardiovascular mortality or HF admission. When CPET ventilatory variables were added to clinical and echocardiographic parameters, prediction of the combined point improved significantly (AUC 0.755 (95% CI 0.662 to 0.832) vs 0.634 (95% CI 0.536 to 0.725), p = 0.016). In conclusion, among elderly female HF patients the CPET derived parameters EOB and VE/VCO_2 slope emerged as strong prognostic markers, with additive predictive value to clinical and echocardiographic parameters in patients with both reduced and preserved LVEF.

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Keywords

Women, Heart Failure, Cardiopulmonary Exercise Test, Ventilatory Inefficiency

1. Introduction

The natural history of heart failure (HF) is different in women and men. In women, HF which develops later in life, is more often attributable to hypertension and less frequent to coronary disease and is more often associated with preserved ventricular function than that in men [1]. Although women with HF have been reported to survive longer [2]-[4], they are admitted to hospital more frequently [5] [6] and present with more severe symptoms than men [3].

The cardiopulmonary exercise test (CPET) provides simultaneous assessment of the performance of the heart, lungs, muscles and cellular respiration during physical exercise and is one of the most reliable tools to select candidates for heart transplantation. Beyond this established role for risk stratification in HF patients, the long-term prognostic value of CPET in women suffering from HF has not yet been deeply explored.

Our study aimed to assess the prognostic value of ventilatory variables for a composite of cardiovascular mortality and HF admissions in a cohort of elderly women with HF and reduced or preserved systolic function.

2. Methods

We studied female patients with a clinical diagnosis of HF based on European Society of Cardiology [7] criteria who were consecutively evaluated at the CPET laboratory of our institution between 2006 and 2011. Patients with both reduced (HFrEF) and preserved (HFpEF) left ventricular ejection fraction (LVEF) were included; patients with preserved (>50%) LVEF had to show signs of congestion on chest X-ray or a BNP value > 100 pg/ml and echocardiographic evidence of diastolic dysfunction [7].

Patients were in NYHA class II-III, on stable pharmacological treatment since at least three months and none of them was a heart transplant candidate. The indication to CPET was risk stratification and clinical decision-making for follow-up planning. Patients were included in the study if they were able to perform a CPET test with a respiratory exchange ratio > 1.00, indicating the achievement of anaerobic exercise conditions. Among 293 considered patients, 82 were ineligible for clinical contraindications to exercise (severe aortic stenosis (n = 10); severe pulmonary disease (n = 6); orthopedic (n = 65) problems; recent onset atrial fibrillation (n = 1)); 80 were excluded for a respiratory exchange ratio < 1.00.

All patients received routine follow-up care. Outcome data of patients who did not attend their scheduled appointments were obtained by telephone interview of the patient or her family: during the follow-up time, none of these patients had been admitted to the hospital. The study was approved by the Institutional Review Board. Subjects signed a written informed consent to the use of their data for scientific purposes.

Standard symptom-limited CPET was performed by cycle ergometry ramping [8]. Analysis was performed with a metabolic cart (Sensor Medics Vmax 29, Yorba Linda, Calif). Before each test, the equipment was calibrated in standard fashion with reference gases. Standard 12-lead ECGs were obtained at rest, each minute during exercise, and for at least 5 minutes during the recovery phase. Blood pressure was measured with a standard cuff sphygmomanometer. Minute ventilation (VE), oxygen uptake (VO_2), carbon dioxide output (VCO_2), and other cardiopulmonary variables were acquired on a breath-by-breath basis and averaged over 10-second intervals. Peak VO_2 (PVO_2) and peak RER were expressed as the highest averaged samples obtained during the exercise test. VE and VCO_2 values were acquired from the initiation of exercise to peak exercise. For the calculation of the slope of minute ventilation/carbon dioxide production linear relationship (VE/VCO_2 slope), we measured all data points from the beginning to the end of exercise [9]. Exercise oscillatory breathing (EOB) was assessed using criteria previously reported by Leite *et al*. [10].

Standard M-mode and two-dimensional echocardiography and Doppler blood flow measurements were performed in agreement with the American Society of Echocardiography guidelines [11] [12]. Early and late diastolic mitral peak flow velocity (E, A) and E-wave deceleration time were assessed by pulsed-wave Doppler echocardiography. Mitral regurgitation was quantitated on a 4-grade (absent, mild, moderate, severe) scale by color-Doppler assessment. In case of at least moderate regurgitation, the PISA method quantification was attempted and insufficiency was classified as severe in the presence of regurgitant surface area ≥ 0.25 cm^2 and/or ≥ 40 mL regurgitant blood volume [11] [12].

Statistical Analysis

Categorical variables are presented as frequency percent and continuous variables as median values [interquartile range]. Between-group differences were tested by chi-square test and Student's *t*-test or non parametric testing according to normal or non normal variable distribution. Study end-point was the combination of cardiovascular mortality or hospital admission for worsening HF. To determine the independent predictors of outcome, we entered variables significant by univariable analysis ($p < 0.05$) in multivariable Cox proportional hazards models. Non categorical variables were dichotomized using literature reference cut offs. Hazard ratios (HR) are presented with 95% confidence intervals (CI). To estimate if the sample size was appropriate for the specific tests, a statistical power analysis [13] was performed ex-post on the main predictors identified and adjusted by the other covariates and the estimated event rate.

Model discrimination was then tested using the c statistic and expressed as area under the ROC curve (AUC). First we derived models including clinical and echocardiographic variables; then we assessed changes in AUC after entering CPET parameters by the method of De Long *et al.* [14]. A p value < 0.05 was considered statistically significant. All statistical tests were two-tailed. Data were analyzed using The Statistical Package for the Social Sciences SPSS 20.

3. Results

We studied 131 stable female HF outpatients after implementation of recommended drug therapy including renin-angiotensin system inhibitors in 131 (100%) and beta-blockers in 64 (50%). Cardiac resynchronization therapy and a cardioverter defibrillator had been previously implanted in 5 patients (4%) who met guideline indications for device therapy.

Clinical characteristics and CPET parameters by LV function are summarized in **Table 1**. Patients with HFpEF and HFrEF had similar age, symptom severity, body mass index, prevalence of atrial fibrillation, achieved workload and VE/VCO_2 slope. Patients with HFrEF showed a higher prevalence of ischemic etiology, left bundle branch block, beta-blocker treatment, moderate-to-severe mitral regurgitation, EOB than subjects with HFpEF.

During a median follow-up of 18 [interquartile range 8 - 54] months, 20 patients died, 18 (14%) of cardiovascular causes (pump failure 8, sudden death 6, acute myocardial infarction 6) and 2 of cancer, whereas 41 subjects were admitted for worsening HF. Using a time-to-first event approach, overall 39 patients (29.7%) met the combined end-point of cardiovascular mortality or HF admission. Variables significantly associated to the combined endpoint by univariable analysis (**Table 2**) were dichotomized and sequentially entered into multivariable Cox models first combining clinical and echocardiographic variables (model 1) and then adding CPET variables (model 2) (**Table 3**). A Cox regression of the log hazard ratio on a covariate with a standard deviation of 0.444 based on a sample of 130 patients achieves, at a 0.05 significance level, 86% power to detect a regression coefficient equal to 1.22 and achieves 89% power to detect a regression coefficient equal to 1.283. The sample size was adjusted since a multiple regression of the main variables of interest on the other covariates (VE/VO_2 slope, atrial fibrillation, LVEF, NYHA class, watts achieved) is expected to have an R-Squared of 0.1130.

In adjusted model 2, the hazard ratio for coexistent EOB and VE/VCO_2 slope > 36 was 8.08 (95% CI 3.01 to 21.7). Adjusted survival rates free from HF admission for patients with neither EOB nor VE/VCO_2 slope > 36, either or both ventilatory abnormalities are shown in **Figure 1**.

We tested the incremental predictive value of adding CPET variables (model 2) to the model including clinical and echocardiographic parameters (model 1): AUC values of model 1 and 2 were 0.634 (95% CI 0.536 to 0.725), and 0.755 (95% CI 0.662 to 0.832), respectively ($p = 0.016$).

4. Discussion

We compared the prognostic value of CPET variables in female patients with HFrEF vs HFpEF. To the best of our knowledge, this is the first report on a large population of elderly HF women to compare the additive predic-

Table 1. Clinical characteristics of the study population.

Variable	All *n* = 131	HFrEF *n* = 61	HFpEF *n* = 70	*p* value
Ischemic etiology	44 (34)	27 (44)	17 (24)	0.017
NYHA class III	31 (24)	12 (21)	19 (27)	0.41
Atrial fibrillation	18 (14)	8 (13)	10 (15)	1.000
Left bundle branch block	31 (26)	26 (47)	5 (8)	0.001
Beta-blockers	64 (50)	37 (62)	27(40)	0.01
Age (years)	72 [62 - 77]	72 [62 - 77]	71 [64 - 79]	0.82
Body mass index	24.2 [22.0 - 27.7]	24.2 [21.7 - 28.9]	24.0 [22.0 - 27.6]	0.85
LVEF (%)	50 [36 - 62]	35 [30 - 41]	61 [55 - 66]	-
E/A ratio	0.77 [0.62 - 142]	0.72 [0.59 - 1.84]	0.80 [0.66 - 1.29]	0.35
Deceleration time	202 [156 - 249]	185 [130 - 240]	209 [175 - 255]	0.26
Restrictive filling pattern	21(16)	14 (23)	7 (10)	0.057
Moderate to severe MR	29 (23)	19 (33)	10 (15)	0.032
Workload (Watt)	52 [40 - 66]	50 [37 - 60]	57 [42 - 71]	0.15
Peak VO_2 (ml/kg/min)	11.3 [9.2 - 13.5]	11.0 [9.0 - 12.5]	11.6 [9.6 - 14]	0.33
% Peak VO_2	52 [42 - 63]	46 [40 - 61]	56 [45 - 63]	0.04
VE/VCO_2 slope	33.9 [30.3 - 41]	34.9 [30.4 - 41.9]	33.2 [29 - 39.8]	0.26
VE/VCO_2 slope > 36	52 (40)	31 (44)	21 (34)	0.28
EOB	52 (40)	36 (51)	16 (31)	0.004

Data are presented as Median [interquartile range] or numbers (%). A, Transmitral A Velocity; E, Transmitral E Velocity; EOB = Exercise Oscillatory Breathing; LBBB = Left Bundle Branch Block; LVEDVI = Left Ventricular End Diastolic Volume Index; LVEF = Left Ventricular Ejection Fraction; LVESVI = Left Ventricular End Systolic Volume Index; MR = Mitral Regurgitation; PVO_2 = Peak Oxygen Uptake; % PVO_2 = Percent Predicted PVO_2; VE/VCO_2 Slope = Slope of the Regression Line Relating VE to Carbon Dioxide Production.

tive value of CPET for prognosis stratifying by ventricular function. We found that ventilatory parameters, EOB and VE/VCO_2 slope, improved outcome prediction, independently of LV function, beyond established clinical and echocardiographic predictors atrial fibrillation and mitral regurgitation.

Our study describes the prognostic impact of ventilatory parameters in a "real world" female HF population, as demonstrated by the mean age (72 years) and proportion with HFpEF (54%) generally neglected in HF trials.

In our female series, atrial fibrillation and mitral regurgitation were key prognostic determinants, consistently with previous reports, irrespective of sex [15]. HF and atrial fibrillation share the same risk factors and together have a negative synergic impact on prognosis [16], increasing mortality and morbidity both in hospitalised [17] and community patients [16] [18], irrespective of LV function [10] [20]. The unfavourable effect of atrial fibrillation on outcome may be even stronger in women [19] and in HFpEF [20].

On the other hand, global and local LV remodelling in HF is frequently associated with mitral regurgitation which in turn increases left atrial dilation and remodelling with enhanced risk of atrial fibrillation and clinical events [21].

CPET represent an important risk stratification tool in daily clinical practice even in elderly HF patients not eligible for heart transplant [22], in whom it is safe, feasible and prognostically reliable [23], provided that they are physically able to perform a maximal exercise test. Previous studies addressed gender differences among relatively young populations of heart transplant candidates. Elmariah *et al.* [24] examined the gender effects on PVO_2 and survival in 594 ambulatory HF patients (28% women) and concluded that women had a significantly

Table 2. Univariable predictors of death or HF admission.

	p value	HR	95% CI
EOB	0.001	3.77	1.87 - 7.32
NYHA class III	0.02	3.27	1.56 - 6.89
Moderate-severe MR	0.01	3.15	1.56 - 6.36
Atrial fibrillation	0.007	2.73	1.31 - 5.67
VE/VCO_2 slope	0.001	1.07	1.04 - 1.10
Watt	0.04	0.98	0.96 - 0.99
Age	0.12	1.03	0.99 - 1.06
LVEF	0.69	0.98	0.95 - 1.00
LBBB	0.10	1.79	0.89 - 3.57
BMI	0.15	0.94	0.87 - 1.02
Peak VO_2	0.17	0.93	0.83 - 1.03
Ischemic etiology	0.15	0.62	0.32 - 1.19
E/A ratio	0.11	1.37	0.93 - 2.03
Deceleration time	0.21	0.99	0.99 - 1.00
Beta-blockers	0.95	1.02	0.53 - 1.94
% Peak VO_2	0.63	0.99	0.97 - 1.01
Restrictive filling pattern	0.12	1.95	0.84 - 4.53

For abbreviations see Table 1.

Table 3. Cox regression analysis of clinical echocardiographic and ventilatory variables with cardiovascular mortality or heart failure admission.

	p value	beta	HR	95% CI
Clinical + echo (model 1)				
Moderate to severe mitral regurgitation	0.003	1.152	3.16	1.49 - 6.73
Atrial fibrillation vs sinus rhtyhm	0.024	1.068	2.91	1.15 - 7.34
NYHA class III vs I-II	0.800	0.700	2.01	0.92 - 4.41
LVEF >50% vs <50%	0.603	0.194	0.82	0.39 - 1.71
Clinical + echo + CPET (model 2)				
Moderate to severe mitral regurgitation	0.001	1.283	3.61	1.64 - 7.93
EOB	0.002	1.220	3.39	1.58 - 7.26
VE/VCO_2 slope >36 vs <36	0.012	0.973	2.65	1.23 - 6.57
Atrial fibrillation vs sinus rhtyhm	0.08	0.897	2.45	0.89 - 6.77
NYHA class III vs I-II	0.95	0.025	1.03	0.41 - 2.59
LVEF >50% vs <50%	0.11	−0.636	0.53	0.24 - 1.15
Workload achieved >50 vs <50 watts	0.96	−0.019	0.98	0.45 - 2.12

CPET = Cardiopulmonary exercise test. For other abbreviations see Table 1.

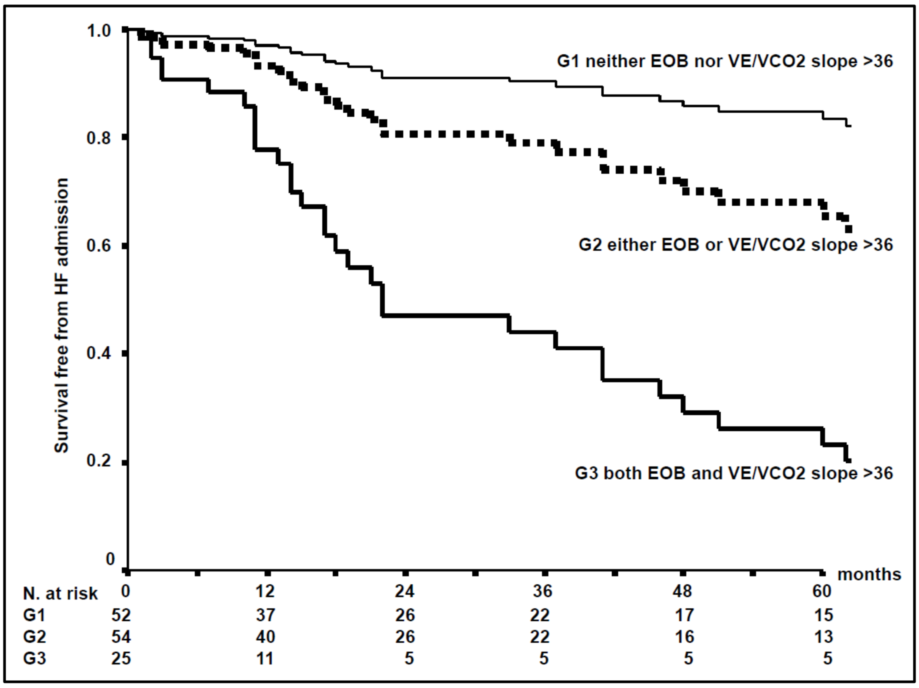

Figure 1. Curves depicting survival free from heart failure admission in relation to absence or presence of one or both ventilatory abnormalities associated with outcome by Cox regression analysis. EOB, exercise oscillatory breating; VE/VCO_2 slope, slope of the regression line relating ventilation to CO_2 output.

lower PVO_2 than men, but had better survival at all levels of exercise capacity and suggested to re-examine the current practice of uniform application of PVO_2 as an aid for transplant timing. This study focused on relatively young female transplant candidates and did not take into account novel ventilatory parameters, such as ventilatory efficiency assessed by the VE/VCO_2 slope during CPET, and EOB. Corrà *et al*. [25] evaluated gender differences in PVO_2 in 529 HF patients (22% women) concluding that in women with HF cut-off PVO_2 values useful for risk stratification should be redefined. Guazzi *et al*. [26] demonstrated that the prognostic value of PVO_2 and VE/VCO_2 slope is similar in men and women with HF and that in both genders the prognostic power of VE/VCO_2 slope is greater than that of PVO_2. Both studies involved women younger than ours (mean age 60 years and 55 years, respectively) and did not consider the incidence and the prognostic weight of EOB.

In a former study among 370 elderly HF patients (29% female), we found a higher EOB prevalence than previously reported in middle-aged cohorts. EOB and the ratio of VE/VCO_2 slope to PVO_2 emerged as the strongest ventilatory predictors of all-cause mortality, independently of ventricular function [27].

EOB is a cyclic breathing pattern that reflects a severe derangement of the ventilatory control system [27]. In previous studies in middle-aged male patient cohorts [28]-[30], prevalence of EOB ranged from 12% to 35% In the only study conducted in patients with diastolic HF [31], EOB was as common as in subjects with systolic dysfunction. In our population, the prevalence of EOB, which has not been previously specifically explored in female HF patients, was 40%, distinctly higher than values reported in transplant candidates (20% - 30%).

The novelty of our study resides first in the population analysed: while women represent over one half of HF patients in the community and show a peculiar phenotype with predominantly preserved LVEF, risk stratification using CPET has been seldom described in a sizable cohort for this patient group. The study by Corrà *et al.* [30] included only 8 women, whereas other reports analysed female cohorts that, although larger, were definitely younger than our patients [28] [29]. Furthermore none of these studies [28]-[30] compared, within the female group, patient with preserved and reduced LVEF. Our findings demostrate that ventricular function does not independently predict prognosis when compaed with ventilatory variables.

We confirmed that prognosis, even for stable female outpatients, is poor: in the medium term one third of patients either died for cardiovascular reasons or was admitted for HF. In agreement with previous data [28]-[31], the ventilatory parameters EOB and VE/VCO_2 slope, emerged as the strongest CPET predictors of outcome in our series, both contributing incremental prognostic value independently of LVEF. We confirmed in elderly women the lack of independent prognostic value of PVO_2 [26] [27] [30] [31]. CPET-derived variables showed an incremental prognostic power when added to clinical and echocardiographic parameters, with very good predictive accuracy as described by the C statistic of 0.755.

4.1. Clinical Implications

The coexistence of ventilatory inefficiency, characterized ed by EOB and incresed VE/VCO_2 slope**,** with moderate to severe mitral regurgitation, identifies, even among female patients, a population with severe circulatory and ventilatory instability, that is associated with a heavy burden of adverse events. Medical management for these women should be reviewed and optimized whenever possible and strict clinical follow-up should be envisaged to recognize early clinical signs of impending destabilization. Regular exercise training, in addition to evidence-based therapy, should be encouraged, on the basis of its safety and the documented decrease in clinical events and improvement in health-related quality of life [32], even in the elderly HF female patient.

4.2. Study Limitations

Our study population was relatively small and included only clinically stable "robust" female outpatients with mild to moderate HF, who did not have important comorbidities and were furthermore able to perform a CPET. We did not include a male patient control group. We did not perform serial CPET to investigate whether patients developed ventilatory abnormalities during follow-up and to assess the impact of optimized treatment on it.

In conclusion, the respiratory pattern during CPET represents a key marker of adverse outcome in female HF patients with both HfrEF and HFpEF. These findings prospect the utility of comprehensively assessing CPET-derived information to optimize the clinical and prognostic work-up of women suffering from HF.

Conflict of Interest

The authors declare no conflict of interest.

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