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Sex Profile and Risk Assessment With Cardiopulmonary Exercise Testing in Heart Failure: Propensity Score Matching for Sex Selection Bias

Ugo Corrà, MD,[a] Piergiuseppe Agostoni, MD, PhD,[b,c,d] Andrea Giordano, PhD,[e] Gaia Cattadori, MD, PhD,[b] Elisa Battaia, MD,[b,f] Rocco La Gioia, MD,[g] Angela B. Scardovi, MD,[h] Michele Emdin, MD,[i] Marco Metra, MD,[j] Gianfranco Sinagra, MD,[k] Giuseppe Limongelli, MD, PhD,[l] Rosa Raimondo, MD,[m] Federica Re, MD,[n] Marco Guazzi, MD, PhD,[o] Romualdo Belardinelli, MD,[p] Gianfranco Parati, MD,[q] Damiano Magrì, MD, PhD,[r] Cesare Fiorentini, MD,[b,c] Mariantonietta Cicoira, MD, PhD,[f] Elisabetta Salvioni, PhD,[b] Marta Giovannardi, MSc,[b] Fabrizio Veglia, PhD,[b] Alessandro Mezzani, MD,[a] Domenico Scrutinio, MD,[g] Andrea Di Lenarda, MD,[s] Roberto Ricci, MD,[h] Anna Apostolo, MD,[b] Anna Maria Iorio, MD,[l] Stefania Paolillo, MD,[t] Pietro Palermo, MD,[b] Mauro Contini, MD,[b] Corrado Vassanelli, MD, PhD,[f] Claudio Passino, MD,[i,u] Pantaleo Giannuzzi, MD,[a] and Massimo F. Piepoli, MD, PhD;[v] on behalf of the MECKI Score Research Group*

[a] *Department of Cardiac Rehabilitation, Salvatore Maugeri Foundation, IRCCS, Veruno (NO), Italy;* [b] *Cardiology Center of Monzino, IRCCS, Milan, Italy;* [c] *Department of Clinical Sciences and Community Health, Cardiovascular Section, University of Milan, Milan, Italy;* [d] *Department of Respiratory and Critical Care Medicine, University of Washington, Seattle, Washington, USA;* [e] *Bioengineering Department, Salvatore Maugeri Foundation, IRCCS, Veruno (NO), Italy;* [f] *Section of Cardiology, Department of Medicine, University of Verona, Verona, Italy;* [g] *Division of Cardiology, Salvatore Maugeri Foundation, IRCCS, Institute of Cassano Murge, Bari, Italy;* [h] *Cardiology Department, Ospedale S. Spirito, Roma Lungotevere in Sassia 3, Roma, Italy;* [i] *Fondazione Gabriele Monasterio, CNR-Regione Toscana, Pisa, Italy;* [j] *Department of Cardiology, Department of Medical and Surgical Specialities, Radiological Sciences, and Public Health, University of Brescia, Brescia, Italy;* [k] *Cardiovascular Department, Ospedali Riuniti and University of Trieste, Trieste, Italy;* [l] *Cardiologia SUN, Ospedale Monaldi (Azienda dei Colli), Seconda Università di Napoli, Napoli, Italy;* [m] *Fondazione Salvatore Maugeri, IRCCS, Istituto Scientifico di Tradate, Dipartimento di Medicina e Riabilitazione Cardiorespiratoria Unità Operativa di Cardiologia Riabilitativa, Tradate, Italy;* [n] *Cardiology Division, Cardiac Arrhythmia Center and Cardiomyopathies Unit, St. Camillo-Forlanini Hospital, Roma, Italy;* [o] *Department of Medical Sciences, Cardiology, IRCCS San Donato Hospital, University of Milan, San Donato Milanese, Milano, Italy;* [p] *Cardiologia Riabilitativa, Azienda Ospedali Riuniti, Ancona, Italy;* [q] *Department of Health Science, University of Milano Bicocca and Department of Cardiology, S. Luca Hospital, Istituto Auxologico Italiano, Milano, Italy;* [r] *Dipartimento di Medicina Clinica e Molecolare, "Sapienza" Università degli Studi di Roma, Roma, Italy;* [s] *Centro Cardiovascolare, Azienda per i Servizi Sanitari n° 1, Trieste, Italy;* [t] *Department of Advanced Biomedical Sciences, University of Naples Federico II University, Naples, Italy;* [u] *Scuola Superiore S. Anna, Pisa, Italy;* [v] *UOC Cardiologia, G da Saliceto Hospital, Piacenza, Italy*

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ABSTRACT

Background: In heart failure (HF), women show better survival despite a comparatively low peak oxygen consumption ($\dot{V}o_2$): this raises doubt

RÉSUMÉ

Introduction : Lors d'insuffisance cardiaque (IC), les femmes présentent une meilleure survie en dépit d'une consommation max-

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*Other MECKI Score Group members can be found in Supplemental Appendix S1.

Corresponding author: Dr Piergiuseppe Agostoni, Centro Cardiologico Monzino, IRCCS, Department of Clinical Sciences and Community Health, Cardiovascular Section, University of Milan, Via Parea, 4 20138 Milan, Italy. Tel.: 0039-02-58002772; fax: 0039-02-502008.

E-mail: piergiuseppe.agostoni@unimi.it or piergiuseppe.agostoni@ccfm.it

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about the accuracy of risk assessment by cardiopulmonary exercise testing (CPET) in women. Accordingly, we aimed to check (1) whether the predictive role of well-known CPET risk indexes, ie, peak $\dot{V}O_2$ and ventilatory response ($\dot{V}E/\dot{V}CO_2$ slope), is sex independent and (2) if sex-related characteristics that impact outcome in HF should be considered as associations that may confound the effect of sex on survival.

Methods: The study population consisted of 2985 patients with HF, 498 (17%) of whom were women, from the multicentre Metabolic Exercise Test Data Combined with Cardiac and Kidney Indexes (MECKI): the end point was cardiovascular death within a 3-year period.

Results: During the follow-up, 305 (12%) men and 39 (8%) women ($P = 0.005$) died, and female sex was linked to better survival on univariate analysis ($P = 0.008$) and independent of peak $\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$ slope on multivariate analysis. According to propensity score matching for female sex to exclude a sex selection bias and sample discrepancy, 498 men were selected: the standardized percentage bias ranged from 20.8 ($P < 0.0001$) to 3.3 ($P = 0.667$). After clinical profile harmonizing, female sex was predictive of HF at univariate analysis.

Conclusions: The low peak $\dot{V}O_2$ and female association with better outcome in HF might be counterfeit: the female prognostic advantage is lost when sex-specific differences are correctly taken into account with propensity score matching, suggesting that for an effective and efficient HF model, adjustment must be made for sex-related characteristics.

imale d'oxygène ($\dot{V}O_2$) relativement faible : cela jette un doute sur la précision de l'évaluation des risques au moyen de l'épreuve d'effort cardiorespiratoire chez les femmes. Par conséquent, nous avions l'objectif de vérifier : 1) si le rôle prédictif des indices de risque bien connus de l'épreuve d'effort cardiorespiratoire, c.-à-d. le $\dot{V}O_2$ maximal et la réponse ventilatoire (pente $\dot{V}E/\dot{V}CO_2$), dépendent du sexe; 2) si les caractéristiques liées au sexe qui ont des répercussions sur l'évolution de l'IC devaient être considérées comme des associations pouvant confondre l'effet du sexe sur la survie.

Méthodes : La population à l'étude comptait 2985 patients, dont 498 (17 %) étaient des femmes, souffrant d'IC selon les indices multicentriques MECKI (Metabolic Exercise Test Data Combined with Cardiac and Kidney Indexes) : le critère de jugement était la mort d'origine cardiovasculaire au cours d'une période de 3 ans.

Résultats : Durant le suivi, 305 (12 %) hommes et 39 (8 %) femmes ($P = 0{,}005$) sont morts, et le sexe féminin était lié à une meilleure survie à l'analyse univariée ($P = 0{,}008$) et indépendant du $\dot{V}O_2$ maximal et de la pente $\dot{V}E/\dot{V}CO_2$ à l'analyse multivariée. En fonction de l'appariement par score de propension selon le sexe féminin pour exclure le biais de sélection lié au sexe et la divergence de l'échantillon, 498 hommes étaient sélectionnés : le biais normalisé exprimé en pourcentage variait de 20,8 ($P < 0{,}0001$) à 3,3 ($P = 0{,}667$). Après l'harmonisation du profil clinique, le sexe féminin était un prédicteur de l'IC à l'analyse univariée.

Conclusions : Le faible $\dot{V}O_2$ maximale et l'association du sexe féminin à une meilleure évolution de l'IC seraient faux : l'avantage pronostique lié au sexe féminin est perdu lorsque les différences entre les sexes sont correctement prises en considération par l'appariement par score de propension, ce qui suggère que pour un modèle d'IC efficace et efficient l'ajustement doit tenir compte des caractéristiques liées au sexe.

The prognostic value of cardiopulmonary exercise testing (CPET) in heart failure (HF) has been established in predominantly male cohorts,[1] whereas research documents that in women with HF, a comparatively flawed gas exchange exercise profile is associated with a better outcome.[2-7] This finding raises some doubt about the accuracy of risk assessment by CPET in women with HF,[8] even though a low female sample size and selection criteria might have distorted the result of our study.

The present study was designed to ascertain (1) whether the predictive role of well-known CPET risk indexes, ie, peak oxygen consumption (peak $\dot{V}O_2$) and ventilatory response ($\dot{V}E/\dot{V}CO_2$ slope) is sex independent and (2) if sex-related characteristics that impact outcome in HF should be considered as associations that may confound the effect of sex on survival.[9-11]

Methods

Study population

The study population was drawn from the database of the ongoing multicentre **M**etabolic **E**xercise Test Data Combined With **C**ardiac and **K**idney **I**ndexes (MECKI) trial,[12] which consists of consecutive patients with HF caused by systolic dysfunction who were prospectively recruited and followed. MECKI exclusion criteria were adopted, plus the following veto conditions: peak respiratory exchange ratio (RER) ≤ 1.00, exercise limitation other than for fatigue or dyspnea, echocardiographic left ventricular ejection fraction (LVEF) $> 40\%$, peak $\dot{V}O_2 > 21$ mL/kg/min, and CPET performed on a treadmill.

Data collection and management

The Cardiology Centre of Monzino was the coordinating centre, whereas individual investigators were responsible for their own records. The following parameters were analyzed at the time of CPET: patient demographics, cause of HF, resting cardiac rhythm, New York Heart Association (NYHA) class, resting LVEF on echocardiography, lifesaving HF therapies, and blood chemistry data. CPET was performed on an electronically braked cycle ergometer with a ramp protocol. Peak $\dot{V}O_2$ was measured in the last 30 seconds of the exercise phase, as was peak RER. The ventilatory anaerobic threshold (VAT) was measured by V-slope analysis of $\dot{V}O_2$ and CO_2 production ($\dot{V}CO_2$)[13] and confirmed by ventilatory equivalents and end-tidal pressures of CO_2 and O_2. The $\dot{V}E/\dot{V}CO_2$ slope (VE is minute ventilation, in liters/minute, and $\dot{V}CO_2$ is CO_2 production, in liters/minute) was calculated as the slope of the linear relationship between $\dot{V}E$ and $\dot{V}CO_2$ from 1 minute after the beginning of the loaded exercise until the end of the isocapnic buffering period. The predicted value of peak $\dot{V}O_2$ was calculated according to Wasserman et al.[14]: predicted peak $\dot{V}O_2$ ($pp\dot{V}O_2$) = (height − age)*20 if male/*14 if female.

Patient follow-up and prognosis

The study end point was cardiovascular death (CVD), and the follow-up ended at 1095 days (ie, 3 years) for censored patients. Events were recorded at the follow-up visits; if a patient did not show up at the scheduled follow-up visit, the patient or family was contacted by phone. If a patient died outside the hospital, medical records of the event and a report of the cause of death were analyzed, and patients who died of noncardiovascular-related causes were censored at the time of the event. Heart transplantation (HT) was not an end point in order to exclude sex selection and therapeutic bias.[15]

Statistical analysis

Continuous data were expressed as means ± standard deviation, whereas categorical data were summarized as counts and percentages. Characteristics of the sex subgroups (men vs women) were compared using unpaired Student t tests for continuous variables and the χ^2 test for discrete variables. Statistical significance was defined as $P < 0.05$.

The prognostic influence of sex was analyzed in the total study population and in a propensity score–matched (PSM) cohort to exclude a sex selection bias and sample discrepancy.[16] The female PSM cohort was calculated using logistic regression analysis with 1:1 matching without replacement. Twenty-one variables were included in the PSM model: age; body mass index (BMI); NYHA class; ischemic cause of HF; baseline cardiac rhythm (presence of atrial fibrillation); LVEF; prescription of amiodarone, loop diuretic, β-blockers, angiotensin-converting-enzyme inhibitors, angiotensin II receptor blockers, and digitalis; presence of an implantable cardioverter defibrillator (ICD), peak $\dot{V}O_2$; $\dot{V}E/\dot{V}CO_2$ slope; VAT identification; peak RER; and serum creatinine, potassium, hemoglobin, and serum sodium concentrations. Adequacy of propensity score matching was assessed by standardized percentage bias for full or matched subsamples.[17] Univariate and multivariate Cox regression models were performed in both the total population and the PSM cohort; a multivariate analysis model included female sex and peak $\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$ slope.

All analyses were performed using STATA IC statistical package, version 11.2 (StataCorp LP, College Station, TX).

Results

We screened 3874 patients from the MECKI score database: 3279 (85%) were men and 595 (15%) were women. According to our study eligibility criteria, 2985 patients with HF were included in the study, 498 (17%) of whom were women: 792 (24%) men and 97 (16%) women were withdrawn. One hundred twenty-nine patients (100 men and 29 women were excluded for LVEF > 40%, 370 patients (351 men and 19 women) for peak $\dot{V}O_2 > 21$ mL/kg/min, 230 patients (201 men and 29 women) for peak RER < 1.05, and 160 patients (140 men and 20 women) for CPET performed on a treadmill.

As Table 1 shows, women with HF were younger and had a lower BMI, incidence of AF and ischemic cause of HF, and a higher mean LVEF than did men with HF. Amiodarone, loop diuretics, and antialdosterone drugs were prescribed less often in women and ICDs were implanted less often. Although mean NYHA class was similar, women showed a lower peak $\dot{V}O_2$, percentage of detectable VAT, $\dot{V}O_2$ (mL/kg/min) measured at VAT, and peak RER, whereas the $\dot{V}E/\dot{V}CO_2$ slope was comparable. Moreover, and as expected, the percentage of pp $\dot{V}O_2$ was higher in women (61% ± 17% vs 54% ± 16% for men; $P <$ 0.0001). Finally, lower serum creatinine, potassium, and hemoglobin values were found in women.

Table 1. Patients' demographic, clinical, blood chemistry, ergospirometry characteristics, and follow-up and events rates according to sex

Variable	Men	Women	P value
Number	2487	498	
Age (y)	63 ± 11	61 ± 12	0.006
Body mass index (kg/m^2)	27 ± 4	26 ± 5	0.000
NYHA class (I-IV)	2.2 ± 0.6	2.2 ± 0.6	0.485
Atrial fibrillation (%)	423 (17)	58 (12)	0.003
Ischemic cause of heart failure (%)	1404 (56)	132 (27)	0.000
Left ventricular ejection fraction (%)	29 ± 7	31 ± 7	0.000
Implanted cardioverter defibrillator (%)	872 (35)	116 (12)	0.000
ACE inhibitor (%)	1897 (76)	363 (73)	0.121
Angiotensin II receptors blocker (%)	452 (18)	107 (22)	0.085
β-Blocker (%)	2114 (85)	418 (84)	0.545
Loop diuretic (%)	2125 (85)	408 (82)	0.046
Antialdosterone drugs (%)	1412 (74)	243 (49)	0.001
Digoxin (%)	587 (24)	98 (20)	0.055
Amiodarone (%)	672 (27)	101 (20)	0.002
Nonidentified VAT (%)	516 (16)	136 (23)	0.000
$\dot{V}O_2$ at VAT (mL/kg/min)*	9.7 ± 2.7	9.2 ± 2.6	0.000
Peak $\dot{V}O_2$ (mL/kg/min)	13.9 ± 3.4	12.8 ± 3.3	0.000
$\dot{V}E/\dot{V}CO_2$ slope	34 ± 7	33 ± 7	0.123
Peak RER	1.13 ± 0.1	1.12 ± 0.1	0.043
Serum creatinine (mg/dL)	1.24 ± 0.4	1.00 ± 0.3	0.000
Serum sodium (mEq/L)	139 ± 3	139 ± 3	0.357
Serum potassium (mEq/L)	4.3 ± 0.4	4.2 ± 0.4	0.000
Hemoglobin (g/dL)	13.7 ± 1.6	12.8 ± 1.2	0.000
Duration of follow-up (d)	846 ± 333	847 ± 334	0.904
Events	305 (12)	39 (8)	0.005

Data are expressed as mean value ± standard deviation or number (%) of patients.

NYHA, New York Heart Association; RER, respiratory exchange ratio; $\dot{V}O_2$, oxygen consumption; $\dot{V}E$, ventilation; $\dot{V}CO_2$, CO_2 production; VAT, ventilatory anaerobic threshold.

*$\dot{V}O_2$ measured when VAT is detected.

During the 3-year follow-up, 305 (12%) men and 39 (8%) women ($P = 0.005$) died. Female sex was linked to a better survival on univariate analysis, with a hazard ratio (HR) of 0.63 ± 0.10 and a 95% confidence interval (CI) of 0.45-0.88 ($P = 0.008$). On multivariate analysis, the female sex protective trait was independent of peak $\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$ slope (Table 2): the model likelihood ratio (LR) χ^2 was 116.74 ($P < 0.001$).

According to propensity score matching, 498 men were selected. Matching was excellent: the standardized percentage bias was reduced from 20.8% ($P < 0.0001$) to 3.3% ($P =$ 0.667). Covariate variance bias before and after propensity score matching is shown in Figure 1. In the PSM cohort, outcome was comparable: 52 (10%) men and 39 (8%) women died. The female sex outcome benefit was not significant on univariate analysis (HR, 0.76 ± 0.15; 95% CI, 0.48-1.11; $P = 0.147$). When forced, the multivariate analysis showed that female sex was not prognostically informative, and only the $\dot{V}E/\dot{V}CO_2$ slope was (Table 2) . The LR χ^2 of this model was 26.9 ($P < 0.001$).

Table 2. CPET variable and gender multivariable analysis model in the overall population and in the PSM cohort

Variables	HR and SD	95% CI	*P* value
Overall population			
Peak $\dot{V}O_2$	0.83 ± 0.02	0.78-0.89	0.000
$\dot{V}E/\dot{V}CO_2$ slope	1.05 ± 0.00	1.03-1.06	0.000
Female gender	0.58 ± 0.12	0.78-0.89	0.010
PSM cohort			
Peak $\dot{V}O_2$	0.93 ± 0.05	0.83-1.05	0.281
$\dot{V}E/\dot{V}CO_2$ slope	1.07 ± 0.01	1.03-1.10	0.000
Female gender	0.71 ± 1.78	0.43-1.16	0.175

CI, confidence interval; CPET, cardiopulmonary exercise testing; HR, hazard ratio; PSM, propensity score-matched; SD, standard deviation; $\dot{V}E$, ventilation; $\dot{V}CO_2$, CO_2 production; $\dot{V}O_2$, oxygen consumption.

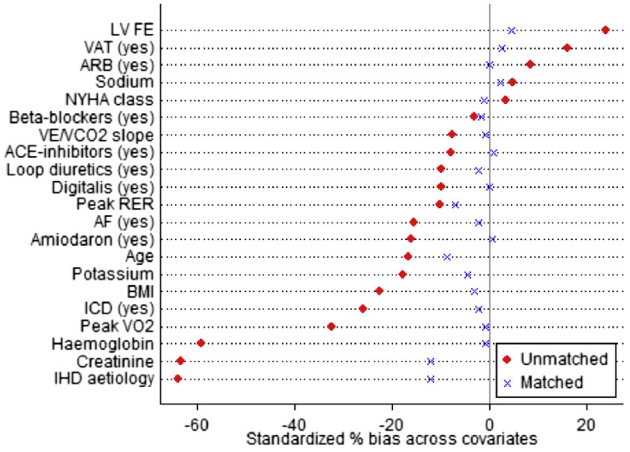

Figure 1. Calibrating plots for sex-related differences, showing variation of standardized percentage bias for all covariates before and after the propensity score adjustment. AF, atrial fibrillation; ARB, angiotensin II receptors blocker; BMI, body mass index; ICD, implantable cardioverter defibrillator; IHD, ischemic heart disease; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RER, respiratory exchange ratio; VAT, ventilatory anaerobic threshold; $\dot{V}E$, ventilation; $\dot{V}CO_2$, CO_2 production; $\dot{V}O_2$, oxygen consumption.

Discussion

Female patients with HF showed a better prognostic outcome in this large cohort derived from the MECKI database, even though peak $\dot{V}O_2$ was comparatively lower than in men. Female sex, peak $\dot{V}O_2$, and the $\dot{V}E/\dot{V}CO_2$ slope had an independent impact on prognosis in the overall population, but after propensity score matching harmonization, the outcome advantage of female sex vanished, whereas the $\dot{V}E/\dot{V}CO_2$ slope conserved its predictive capacity. Because distinctive female factors (eg, biological characteristics) as recruitment criteria and population compendia (eg, selection bias) may individually impact outcome in an intertwined manner, an accurate risk assessment should take into account the sex profile.[12,18-20]

Previous experiences are scant,[2-7] but they all demonstrate that peak $\dot{V}O_2$ is predictive in women with HF despite differences in sample size (generally a low percentage of women with HF are included in CPET trials), selection criteria (LVEF and peak $\dot{V}O_2$), follow-up duration, and type of events. Richard et al.[2] studied young patients with HF (55 men and 21 women) and found that the event-free survival rate for CVD and HT was significantly higher in women. Elmariah et al.[3] examined 594 outpatients with HF, including 28% women: 94% of the women vs 81% of the men attained 1-year transplant-free survival, and female survival was superior in the lower peak $\dot{V}O_2$ classes. Guazzi et al.[4] studied 75 women and 337 men with HF: 1-year event rates were observed in 24% of the female group and 35% of the male group. Green et al.[5] evaluated 278 men and 274 women, and 1-year events were death before HT, implantation of a left ventricular assist device, or inotrope-dependent transplantation (United Network of Organ Sharing status 1, 1A, or 1B). Event-free survival was similar between women and men, but women had better survival for a given peak $\dot{V}O_2$. Hsich et al.[6] studied 2105 patients with HF, 525 (25%) of whom were women: during the 5-year follow-up, 129 women (26%) and 572 men (36%) died (all-cause mortality), but women were at lower risk of death for any given peak $\dot{V}O_2$ value. Finally, Corrà et al.[7] investigated 529 patients with HF (116 women) with peak $\dot{V}O_2 \leq 14$ mL/kg/min, ie, mean peak $\dot{V}O_2$ 11.2 ± 1.9 mL/kg/min: 2-year event free survival without CVD or urgent HT was higher in women (85% vs 66%). As a final point, women live longer even though peak $\dot{V}O_2$ is comparatively lower. Despite this, women showed a distinctive clinical profile, and several sex-specific features could impact outcome per se.[2-7,21-23] Sex profile mismatching could be partially related to inclusion/exclusion criteria and partially to a conventional way of acting in CPET studies; we believe that propensity score matching for female sex might close this gap.

The present study represents the largest CPET population (second in terms of number of women enrolled) treated with updated therapy for HF, and the primary end point was cardiovascular mortality to avoid sex bias regarding HT selection. Clinical and exercise characteristics of female patients were almost similar to those reported in previous studies,[2-7] although better HF treatment (pharmacologic and device therapy) was witnessed (Table 3). We confirmed that the percentage of women enrolled is low and that women have particular features (eg, younger age, higher mean LVEF, lower mean peak $\dot{V}O_2$ at the same peak RER but a higher percent pp $\dot{V}O_2$). Briefly, the "best" clinical and "exercising" women are usually registered in HF and CPET studies, making most characteristics not replicable in "general" HF trials.[22] Unsurprisingly, a low event rate was witnessed: in the general population, female sex, peak $\dot{V}O_2$, and the $\dot{V}E/\dot{V}CO_2$ slope were each independent predictors. Female patients showed a better survival, even though peak $\dot{V}O_2$ was lower than in men.[2-7] Conversely, several sex attributes, over and above peak $\dot{V}O_2$, in the main study population differed, eg, women were younger and had lower BMI; incidence of a nonischemic HF cause, and atrial fibrillation; were treated less often with antialdosterone drugs; and had higher LVEF. All these features might distort and confound the relationship between survival and peak $\dot{V}O_2$ in women with HF, eg, a low peak $\dot{V}O_2$ (negative risk factor) could be balanced by a nonischemic cause of HF in the presence of sinus rhythm (protective effect). Propensity score matching for female sex was performed to abate the difference in biological and sex selection. In the PSM cohort, the female outcome benefit was lost, even though the percent pp $\dot{V}O_2$ difference was still evident by sex (55% ± 15% vs 61% ± 16% in men and women,

Table 3. Summary table of main demographics and clinical and functional characteristics of "sex" studies on CPET and outcomes

	Richards et al.[2]		Elmariah et al.[3]		Guazzi et al.[4]		Green et al.[5]		Hsich et al.[6]		Corrà et al.[7]	
Variable	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
No. of patients (%)	55 (72)	21 (28)	427 (72)	167 (28)	337 (82)	75 (18)	278 (51)	274 (49)	1580 (88)	214 (12)	413 (79)	116 (21)
Age (y)	51 ± 12	49 ± 9	53 ± 12	49 ± 1*	57 ± 13	55 ± 12	55 ± 11	52 ± 13	51 ± 12	51 ± 12	60 ± 11	60 ± 9
NYHA class	2.7 ± 0.9	2.6 ± 0.9	NA	NA	2.2 ± 0.6	2.3 ± 0.8	NA	NA	NA	NA	NA	NA
IHD (%)	60	33*	43	15*	55	52	51	26*	43	22*	66	55*
AF (%)	NA	NA	15	3*	NA	NA	NA	NA	7	3	13	7
DM (%)	NA	NA	26	16*	NA	NA	NA	NA	25	25	NA	NA
ICD (%)	NA	NA	16	5*	NA	NA	NA	NA	20	17	35	28
ACE inhibitors (%)	NA	NA	78	74	72	73	87	81	83	79	92	90
Loop diuretics (%)	NA	NA	70	74	53	63	NA	NA	84	84	92	87
β-blockers (%)	NA	NA	73	72	42	39	60	54	44	44	53	58
LVEF (%)	19 ± 9	20 ± 11	25 ± 11	29 ± 13*	33 ± 11	32 ± 13	27 ± 11	29 ± 13	20 ± 15	20 ± 15	22 ± 7	27 ± 7*
Peak $\dot{V}O_2$ (mL/kg/min)	18.3 ± 5	14.5 ± 2*	16.6 ± 7	14 ± 4*	17.1 ± 5	12.8 ± 3*	17.1 ± 5	13.9 ± 5*	16	15	11.4 ± 1.9	10.6 ± 1.9*
Percent pp $\dot{V}O_2$ (%)	65 ± 18	75 ± 16	NA	NA	NA	NA	NA	NA	NA	NA	42 ± 10	53 ± 15*
Peak RER	1.14 ± 0.1	1.08 ± 0.1*	1.11 ± 0.1	1.05 ± 0.1*	1.07 ± 0.1	1.02 ± 0.1*	NA	NA	1.10	1.20	1.14 ± 0.06	1.15 ± 0.07
$\dot{V}E/\dot{V}CO_2$ slope	NA	NA	NA	NA	33 ± 8	37 ± 9*	NA	NA	NA	NA	37 ± 9	35 ± 8

The reference number follows the author's name (see reference list, for details).

ACE, angiotensin-converting enzyme; AF, atrial fibrillation; CPET, cardiopulmonary exercise testing; DM, diabetes mellitus; ICD, implantable cardioverter defibrillator (% of patients with implants); IHD, ischemic cause of heart failure; LVEF, left ventricular ejection fraction; NA, not available; RER, respiratory exchange ratio; $\dot{V}E$, ventilation; $\dot{V}CO_2$, CO_2 production; $\dot{V}O_2$, oxygen consumption.

*Significant difference ($P < 0.05$).

respectively), by definition. Regarding prognosis, sex clinical profile matching seems to prevail over the persistence of exercise capacity discrepancy (higher mean percent pp $\dot{V}O_2$ in women): the negligible predictive role of percent pp $\dot{V}O_2$ in the PSM cohort is intriguing and provoking, because it implies that clinical profile harmonizing is essential for outcome assessment, more so than residual exercise capacity.

Study limitations

First, this study was not designed to evaluate sex risk factors individually and their predictive ability according to a hierarchical approach. Second, the prognostic impact of variables was assessed at a single time point; changes, eg, an upgrading of treatment during follow-up, might have altered the survival analysis and cannot be excluded. Third, the study end point was cardiovascular mortality; other causes of death (ie, sudden cardiac death or worsening of HF) that might be related to sex were not investigated.[24] Fourth, although renal function, hemoglobin, and electrolyte hemostasis were evaluated, other HF-related comorbidities that impact prognosis were not considered. Finally, we excluded patients with HF with preserved LV systolic function, a condition more frequently seen among women.

Conclusions

The association of low peak $\dot{V}O_2$ and better outcomes in women with HF might be false if sex-specific differences are correctly taken into account. Propensity score matching for sex in the clinical profile provides a way for truthful risk assessment, suggesting that for an effective and efficient HF model, adjustments must be made for sex-related characteristics.

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Disclosures

The authors have no conflicts of interest to disclose.

References

1. Corrà U, Piepoli MF, Adamopoulos S, et al. Cardiopulmonary exercise testing in systolic heart failure in 2014: the evolving prognostic role: a position paper from the committee on exercise physiology and training of the heart failure association of the ESC. Eur J Heart Fail 2014;16:929-41.

2. Richards DR, Mehra MR, Ventura HO, et al. Usefulness of peak oxygen consumption in predicting outcome of heart failure in women versus men. Am J Cardiol 1997;80:1236-8.

3. Elmariah S, Goldberg LR, Allen MT, Kao A. Effects of gender on peak oxygen consumption and the timing of cardiac transplantation. J Am Coll Cardiol 2006;47:2237-42.

4. Guazzi M, Arena R, Myers J. Comparison of the prognostic value of cardiopulmonary exercise testing between male and female patients with heart failure. Int J Cardiol 2006;113:395-400.

5. Green P, Lund LH, Mancini D. Comparison of peak exercise oxygen consumption and the Heart Failure Survival Score for predicting prognosis in women versus men. Am J Cardiol 2007;99:399-403.

6. Hsich E, Chadalavada S, Krishnaswamy G, et al. Long-term prognostic value of peak oxygen consumption in women versus men with heart failure and severely impaired left ventricular systolic function. Am J Cardiol 2007;100:291-5.

7. Corrà U, Mezzani A, Giordano A, et al. Peak oxygen consumption and prognosis in heart failure: 14 mL/kg/min is not a "gender-neutral" reference. Int J Cardiol 2013;167:157-61.

8. Mitka M. Gender a factor to consider in weighing timing of heart transplant. JAMA 2006;296:642-3.

9. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012;33:1787-847.

10. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2013;128:e240-327.

11. Stein GY, Ben-Gal T, Kremer A, et al. Gender-related differences in hospitalized heart failure patients. Eur J Heart Fail 2013;15:734-41.

12. Agostoni P, Corrà U, Cattadori G, et al. on behalf of the MECKI score research group. Metabolic exercise test data combined with cardiac and kidney indexes, the MECKI score: A multiparametric approach to heart failure prognosis. Int J Cardiol 2013;167:2710-8.

13. Beaver WL, Wasserman K, Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. J Appl Physiol 1986;60:2020-7.

14. Wasserman K, Hansen JE, Sue DY, Stringer WW, Whipp BJ. Clinical Exercise Testing. Principles of Exercise Testing and Interpretation Including Pathophysiology and Clinical Applications. Philadelphia, PA: Lippincott Williams & Wilkins, 2005:138-9.

15. Hsich EM, Starling RC, Blackstone EH, et al. Does the UNOS heart transplant allocation system favor men over women? J Am Coll Cardiol 2014;2:347-55.

16. D'Agostino RB Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. Stat Med 1998;17:2265-81.

17. Rosenbaum PR, Rubin DB. Constructing a control group using multivariate matched sampling methods that incorporate the propensity score. Am Stat 1985;39:33-8.

18. O'Connor CM, Whellan DJ, Wojdyla D, et al. Factors related to morbidity and mortality in patients with chronic heart failure with systolic dysfunction. The HF-ACTION predictive risk score model. Circ Heart Fail 2012;5:63-71.

19. Chyu J, Fonarow GC, Tseng CH, Horwich TB. Four-variable risk model in men and women with heart failure. Circ Heart Fail 2014;7:88-95.

20. Ouwerkerk W, Voors AA, Zwinderman AH. Factors influencing the predictive power of models for predicting mortality and/or heart failure hospitalization in patients with heart failure. JACC Heart Fail 2014;2:429-36.

21. Ghali JK, Lindenfeld J. Sex differences in response to chronic heart failure therapies. Expert Rev Cardiovasc Ther 2008;6:555-65.

22. Martınez-Sellé M, Doughty RN, Poppe K, et al. on behalf of the Meta-Analysis Global Group In Chronic Heart Failure (MAGGIC). Gender and survival in patients with heart failure: interactions with diabetes and aetiology. Results from the MAGGIC individual patient meta-analysis. Eur J Heart Fail 2012;14:473-9.

23. Lauffenburger JC, Robinson JG, Oramasionwu C, Fang G. Racial/ethnic and gender gaps in the use of and adherence to evidence-based preventive therapies among elderly Medicare Part D beneficiaries after acute myocardial infarction. Circulation 2014;129:754-63.

24. Rho RW, Patton KK, Poole JE, et al. Important differences in mode of death between men and women with heart failure who would qualify for a primary prevention implantable cardioverter-defibrillator. Circulation 2012;126:2402-7.

Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at http://dx.doi.org/10.1016/j.cjca.2015.09.010.