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## Clinical Research

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

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

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

**ABSTRACT**

**Background:** In heart failure (HF), women show better survival despite a comparatively low peak oxygen consumption ( $\dot{V}O_2$ ): this raises doubt about the accuracy of risk assessment by cardiopulmonary exercise testing (CPET) in women. Accordingly, we aimed to check (1) whether

**RÉSUMÉ**

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

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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](mailto:piergiuseppe.agostoni@unimi.it) or [piergiuseppe.agostoni@ccfm.it](mailto:piergiuseppe.agostoni@ccfm.it)

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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.

cardiorespiratoire chez les femmes. Par conséquent, nous avons 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,<sup>1</sup> whereas research documents that in women with HF, a comparatively flawed gas exchange exercise profile is associated with a better outcome.<sup>2-7</sup> This finding raises some doubt about the accuracy of risk assessment by CPET in women with HF,<sup>8</sup> 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.<sup>9-11</sup>

## Methods

### Study population

The study population was drawn from the database of the ongoing multicentre Metabolic Exercise Test Data Combined With Cardiac and Kidney Indexes (MECKI) trial,<sup>12</sup> 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)  $\leq 1.00$ , 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 ( $\dot{V}_{CO_2}$ )<sup>13</sup> 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.<sup>14</sup>: 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

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