International Journal of Cardiology 388 (2023) 131119

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Editorial

More cardiopulmonary effort testing needed in HFpEF!

Heart failure with preserved ejection fraction (HFpEF) is expected to become the most frequent type of HF in the next future, and is associated with significant morbidity and mortality, despite the recent therapeutic advances [1].

The diagnosis of HFpEF, according to the current guidelines, relies on the integration of clinical (symptoms/signs of HF), biohumoral (namely B-type natriuretic peptide plasma elevation), and imaging findings, demonstrating structural and functional cardiac abnormalities [2]. Nevertheless, signs and symptoms of congestion might not be always present in the individual patient, and limited mobility might mask effort-related symptoms [3]. Further, comorbidities (e.g. obesity, kidney insufficiency, chronic obstructive pulmonary disease), which are highly prevalent in HFpEF, may confound the clinical presentation and influence natriuretic peptides concentration [1–3].

To overcome these limits, 2 multiparametric approaches have been proposed to improve diagnostic accuracy in HFpEF: a) the H2FPEF score, developed at the Mayo Clinic to identify the cardiac origin of effort dyspnea in patients with preserved ejection fraction by the evaluation of clinical and imaging variables (obesity, atrial fibrillation, age, antihypertensive treatment, increased filling pressures and systolic pulmonary arterial pressure) [4]; b) the HFA-PEFF algorithm, proposed by the Heart Failure Association (HFA) of the European Society of Cardiology (ESC), consisting of a multiparametric stepwise approach, starting from pre-test clinical assessment to a comprehensive echocardiography and natriuretic peptides assessment [5]. From the integration of functional, morphological, and biohumoral parameters, a score is then calculated and the HFpEF diagnosis either ruled-out (<2) or ruled-in (≥ 5 points), respectively [5]. In the gray zone (2–4 point score), functional testing (echocardiography or invasive hemodynamic exercise stress test), should be performed to solve the uncertainty [5]. Both scores have also shown prognostic significance in HFpEF populations, with higher values being associated with a higher risk of HF-related hospitalization and all-cause mortality [6,7].

With regard to exercise capacity, only the H2PEF score holds a predictive value, as documented by Amani et al., who pointed out the lack of clinical variables as a major flaw of the HFA-PEFF score [8]. A marginal role in the HFA-PEFF algorithm has been attributed to cardiopulmonary exercise test (CPET), recommended only as an optional tool to rule-out noncardiac etiologies of dyspnea, while a larger use of this test should be advisable to obtain additional information both for diagnostic and prognostic purposes.

In this issue of the *Journal*, Lee et al. tested this hypothesis on a cohort of consecutive patients with dyspnea and preserved ejection fraction ($n = 292$, mean age 58 ± 14 years, 57% males), undergoing a full baseline characterization, including CPET and echocardiography, therefore followed-up for a composite cardiovascular endpoint (including cardiovascular-related mortality, recurrent HF hospitalization, urgent repeat revascularization/myocardial infarction, or any hospitalization due to cardiovascular events) [9]. According to the HFA-PEFF score, the study population was distinguished into 3 subgroups (<2, $n = 81$; 2–4, $n = 159$, ≥ 5, $n = 52$). At survival analysis, a ≥ 5 score, VE/VCO2 slope, peak systolic strain rate of the left atrium and resting diastolic blood pressure were identified as independent predictors. Notably, the addition of both HFA-PEFF score and VE/VCO2 slope to the prediction model allowed a significant reclassification of patients' risk [9]. Finally, the addition of VE/VCO2 over HFA-PEFF score yielded further incremental prognostic significance, particularly in patients with a < 5 score.

Although currently underutilized in the clinical practice, CPET provides crucial pathophysiological clues, with diagnostic and prognostic implications. Indeed, beyond yielding the same information provided by a traditional exercise stress test (i.e., physical tolerance, symptom occurrence, and ECG abnormalities), CPET allows the unique opportunity of assessing the cardiorespiratory interactions during exercise, unraveling pathophysiological mechanisms in complex disease conditions, such as HFpEF [10]. Of note, in the study of Lee et al. [9], only VE/VCO2 retained independent and incremental prognostic value. This findings confirm and extend those of an ancillary study by Guazzi et al. [11], showing that VE/VCO2, but not peak VO2, was an independent predictor of adverse events in patients with HFpEF [11]. Although a definitive explanation is missing, the stronger prognostic value of VE/VCO2, an index of ventilatory efficiency, underscores the importance of evaluating by means of CPET in HFpEF patients the complex interaction between gas exchanges, systemic and pulmonary vasculature, cardiac and skeletal muscle function, influencing the adaptation to exercise in pathophysiological conditions, finally limiting physical tolerance [10,11].

Interestingly, the integration of CPET with echocardiography has been recently proposed as a unique, noninvasive, comprehensive approach, providing at a same time information regarding both the cardiorespiratory and hemodynamic changes occurring during exercise [10]. Although only a few Centers worldwide routinely perform this combined test, the growing evidence about its accuracy in the diagnostic setting and in risk stratification, alongside to the progressive standardization of the proposed protocols, may lead to a larger use of this valuable testing modality in the next years.

DOI of original article: https://doi.org/10.1016/j.ijcard.2023.05.038.

https://doi.org/10.1016/j.ijcard.2023.131119
Received 10 June 2023; Accepted 12 June 2023
Available online 14 June 2023

Until then, given the crucial incremental prognostic value provided, further confirmed by Lee et al. [9], a larger implementation of CPET in the diagnostic armamentarium may represent a key step to improve the management of patients with HFpEF, also considering the recent availability of disease-modifying treatment, such as sodium-glucose co-transporter 2 inhibitors (SGLT2i) [2]. Finally, to further improve risk stratification, a multiparametric score integrating CPET parameters and easy-to-obtain clinical, laboratory, and echocardiographic variables (the MECKI score) showed high accuracy in patients with HF and reduced ejection fraction [12]. Given the recent findings of Lee et al. [9], the development and validation of a similar score in HFpEF patients may therefore have a great clinical impact.

Declaration of Competing Interest

The authors report no relationships that could be construed as a conflict of interest.

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Francesco Gentile[a,b,*], Alberto Giannoni[a,b], Michele Emdin[a,b], Iacopo Fabiani[b]

[a] *Health Science Interdisciplinary Center, Scuola Superiore Sant'Anna, Pisa, Italy*

[b] *Fondazione Toscana G. Monasterio, Pisa, Italy*

[*] Corresponding author at: Scuola Superiore Sant'Anna, Fondazione Toscana G. Monasterio CNR-Regione Toscana, via Giuseppe Moruzzi 1, 56124 Pisa, Italy.

E-mail address: francesco.gentile@santannapisa.it (F. Gentile).