JACC: ADVANCES VOL. 3, NO. 7, 2024

EDITORIAL COMMENT

Sex-Related Determinants of Exercise Intolerance in HFpEF

Not Just a Matter of the Heart!

Lavinia Del Punta, MD, Nicolò De Biase, MD, Nicola Riccardo Pugliese, MD, PhD

Heart failure (HF) with preserved left ventricular ejection fraction (HFpEF) is quickly becoming the most prevalent phenotype of HF[1] and is one of the most significant unmet needs in contemporary medicine.[2] Indeed, HFpEF presents physicians with several arduous challenges, including remarkable difficulties in accurate diagnosis and a scarce response to current medical therapy, with few exceptions.[2,3] As the outcomes of these patients remain relatively poor,[1] deeper insight into the ill-defined mechanisms subtending the development and progression of HFpEF would be crucial to implementing new therapeutic strategies. The "traditional" HFpEF phenotype is characterized by the association with female sex, older age, and several traditional cardiovascular risk factors and comorbidities, such as arterial hypertension, diabetes mellitus, dyslipidemia, visceral obesity, pulmonary disease, and chronic kidney disease. However, multiple diverse pathophysiologic derangements seem to delineate different HFpEF subphenotypes, including impaired systolic and diastolic function (especially during exercise), atrial dysfunction, abnormal autonomic tone, and alterations in peripheral mechanisms such as endothelial and skeletal muscle function.[4-7]

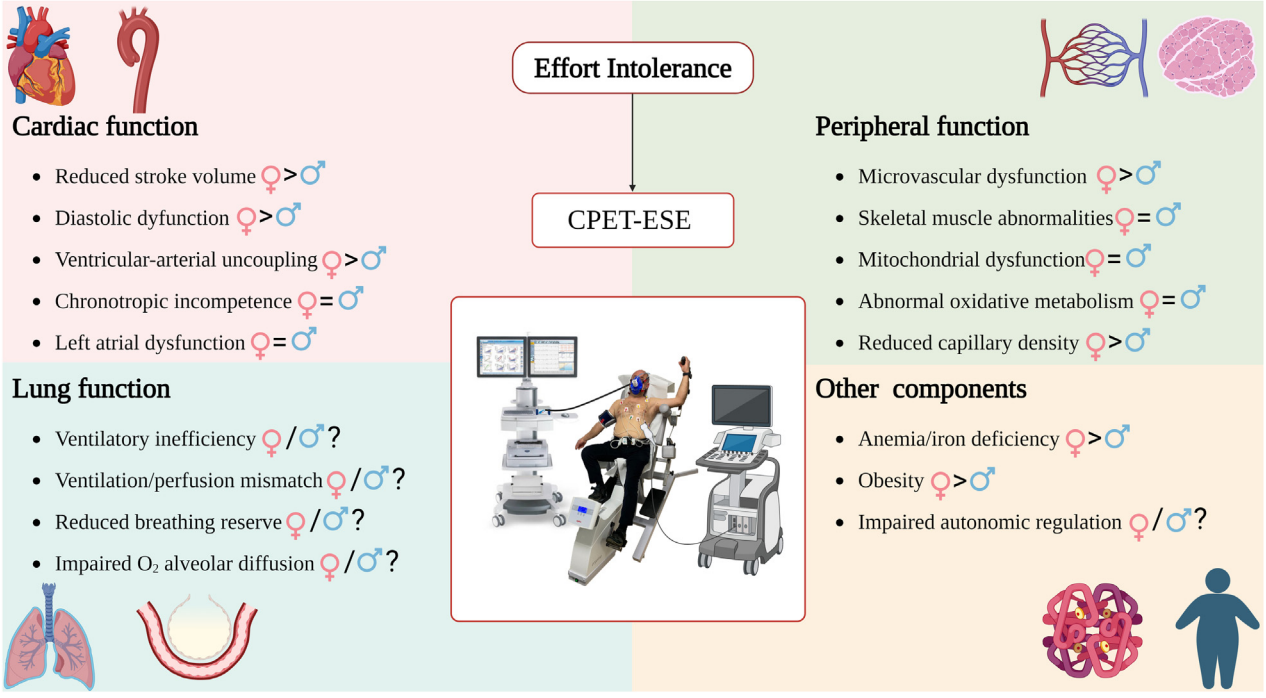
In recent years, the question of whether biological sex may represent a novel key in the pathophysiology of HFpEF has gained remarkable attention in the research setting[8-11]; indeed, the heterogeneity observed in HFpEF could partially depend on sex-related differences in the regulation of cardiovascular and metabolic processes[12,13] (**Figure 1**). Verwerft et al[14], in this issue of *JACC: Advances*, address such a topic in the present issue of this journal, analyzing the determinants of functional capacity in a large population of patients undergoing cardiopulmonary exercise testing with simultaneous exercise-stress echocardiography for unexplained dyspnea. The likelihood of HFpEF for each patient was assessed with either the H2FPEF or HFA-PEFF score.[15,16] Females and males were compared in the total population and according to HFpEF likelihood (ie, positive vs negative HFpEF scores). As a curious finding, there was a relatively low prevalence of typical comorbidities of HFpEF (ie, arterial hypertension, diabetes mellitus, and atrial fibrillation) in the general population.[14] However, probability scores might have limited sensitivity, especially in early disease stages[17]; exercise testing is often useful to refine the diagnostic work-up of suspected HFpEF,[18] and was appropriately used in the research protocol for patients evaluated with HFA-PEFF score. HFpEF was defined as likely in 29% (n = 555) of patients based on a positive HFA-PEFF or H2FPEF score, with a significantly higher prevalence in females (34%, n = 321) than males (24%, n = 234). Unfortunately, invasive hemodynamic evaluation at rest and exercise was not available to confirm the diagnosis of HFpEF, nor were alternative diagnoses formulated for patients with a low HFpEF probability.[14]

Regardless of HFpEF likelihood, peak oxygen consumption (VO_2) was systematically lower in women than men, resulting from both reduced estimated oxygen delivery—due to smaller peak stroke volume (even when indexed for body surface area) and hemoglobin levels—and reduced arteriovenous oxygen difference (AVO_2diff).[14] To our knowledge, previous invasive and noninvasive studies in patients

From the Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy.
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 2772-963X https://doi.org/10.1016/j.jacadv.2024.101038

FIGURE 1 Sex-Dependent Differences in Determinants of Exercise Intolerance, According to Different Pathophysiological Domains



CPET = cardiopulmonary exercise testing; ESE = exercise-stress echocardiography.

with HFpEF had found no significant sex-related difference after indexing stroke volume to body surface area, neither at rest nor peak exercise.[10,19] Thus, the observed abnormality in the central component of VO_2 (*ie*, cardiac systolic function) in women compared to men should be further investigated. On the other hand, the increase in estimated left ventricular stiffness reported in women, indicating more advanced diastolic dysfunction, is in keeping with the existing literature.[10] Another notable finding is that women also display a peripheral oxygen extraction (AVO_2diff) impairment, which appears to be mediated by lower estimated arterial oxygen content and lower estimated muscle diffusive oxygen conductance. Defects in oxygen uptake and utilization are key determinants of effort intolerance in HFpEF,[20] but no solid data about sex-dependent differences in such mechanisms are available. Partially limited by the non-invasive nature of their study, Verwerft et al[14] hypothesize that their results might be explained by decreased capillary density and mitochondrial oxidative capacity, which, however, had been reported in older women and men equally.[21] Interestingly, iron deficiency was more prevalent in females,[14] and might further explain blunted oxygen utilization in this group.[22] Finally, the Authors found no significant differences in lung function between men and women regardless of HFpEF probability; however, they only evaluated breathing reserve. Thus, the contribution of sex-dependent ventilatory abnormalities to the pathophysiology of HFpEF remains to be clearly elucidated.

In conclusion, the paper by Verwerft et al[14] adds to the growing evidence regarding the association between the female sex and peculiar alterations in both central and peripheral components of VO_2 that may contribute to an increased risk of developing exercise intolerance and, ultimately, HFpEF. Confirming the nature and extent of such sex-dependent pathophysiologic differences could ultimately pave the way for truly personalized therapeutic approaches.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Nicola Riccardo Pugliese, Department of Clinical and Experimental Medicine, University of Pisa, Via Roma, 67, Pisa 56126, Italy. E-mail: n.r.pugliese88@gmail.com.

REFERENCES

1. Savarese G, Becher PM, Lund LH, Seferovic P, Rosano GMC, Coats AJS. Global burden of heart failure: a comprehensive and updated review of epidemiology. *Cardiovasc Res*. 2023;118:3272–3287.

2. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail*. 2022;24:4–131.

3. Pugliese NR, Pellicori P, Filidei F, et al. Inflammatory pathways in heart failure with preserved left ventricular ejection fraction: implications for future interventions. *Cardiovasc Res*. 2023;118:3536–3555.

4. Pugliese NR, De Biase N, Del Punta L, et al. Deep phenotype characterization of hypertensive response to exercise: implications on functional capacity and prognosis across the heart failure spectrum. *Eur J Heart Fail*. 2023;25:497–509.

5. Pugliese NR, Balletti A, Armenia S, et al. Ventricular-arterial Coupling Derived from Proximal aortic stiffness and Aerobic capacity across the heart failure spectrum. *JACC Cardiovasc Imaging*. 2022;15:1545–1559.

6. Kitzman DW, Nicklas B, Kraus WE, et al. Skeletal muscle abnormalities and exercise intolerance in older patients with heart failure and preserved ejection fraction. *Am J Physiol Heart Circ Physiol*. 2014;306:H1364–H1370.

7. De Biase N, Mazzola M, Del Punta L, et al. Haemodynamic and metabolic phenotyping of patients with aortic stenosis and preserved ejection fraction: a specific phenotype of heart failure with preserved ejection fraction? *Eur J Heart Fail*. 2023;25:1947–1958.

8. Lam CSP, Arnott C, Beale AL, et al. Sex differences in heart failure. *Eur Heart J*. 2019;40:3859–3868.

9. Packer M, Lam CSP, Lund LH, Maurer MS, Borlaug BA. Characterization of the Inflammatory-metabolic phenotype of heart failure and a preserved ejection fraction: a Hypothesis to explain Influence of sex on the Evolution and Potential treatment of the disease. *Eur J Heart Fail*. 2020;22:1551–1567.

10. Gori M, Lam CSP, Gupta DK, et al. Sex-specific cardiovascular structure and function in heart failure with preserved ejection fraction. *Eur J Heart Fail*. 2014;16:535–542.

11. Petek BJ, Gustus SK, Churchill TW, et al. Sex-based differences in peak exercise Blood pressure indexed to oxygen consumption Among Competitive Athletes. *Clin Ther*. 2022;44:11–22.e3.

12. Fliegner D, Schubert C, Penkalla A, et al. Female sex and estrogen receptor-beta attenuate cardiac remodeling and apoptosis in pressure overload. *Am J Physiol Regul Integr Comp Physiol*. 2010;298:R1597–R1606.

13. Klein SL, Flanagan KL. Sex differences in immune responses. *Nat Rev Immunol*. 2016;16:626–638.

14. Verwerft J, Foulkes S, Bekhuis Y, et al. The oxygen cascade according to HFpEF likelihood: a focus on sex differences. *JACC Adv*. 2024;3:101039.

15. Paulus WJ. H2FPEF Score: at last, a properly validated diagnostic algorithm for heart failure with preserved ejection fraction. *Circulation*. 2018;138:871–873.

16. Pieske B, Tschöpe C, De Boer RA, et al. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). *Eur Heart J*. 2019;40:3297–3317.

17. Sanders-van Wijk S, Barandiarán Aizpurua A, Brunner-La Rocca HP, et al. The HFA-PEFF and H2FPEF scores largely disagree in classifying patients with suspected heart failure with preserved ejection fraction. *Eur J Heart Fail*. 2021;23:838–840.

18. Pugliese NR, De Biase N, Gargani L, et al. Predicting the transition to and progression of heart failure with preserved ejection fraction: a weighted risk score using bio-humoural, cardiopulmonary, and echocardiographic stress testing. *Eur J Prev Cardiol*. 2020;28:1650–1661.

19. Beale AL, Nanayakkara S, Segan L, et al. Sex differences in heart failure with preserved ejection fraction pathophysiology: a detailed invasive hemodynamic and echocardiographic analysis. *JACC Heart Fail*. 2019;7:239–249.

20. Del Punta L, De Biase N, Di Fiore V, et al. Combining cardiopulmonary exercise testing with echocardiography : a multiparametric approach to the cardiovascular and cardiopulmonary systems. *Eur Heart J Imag Methods Pract*. 2023;1:1–12.

21. Coggan AR, Spina RJ, King DS, et al. Histochemical and enzymatic comparison of the gastrocnemius muscle of young and elderly men and women. *J Gerontol*. 1992;47:B71–B76.

22. Charles-Edwards G, Amaral N, Sleigh A, et al. Effect of iron Isomaltoside on skeletal muscle Energetics in patients with chronic heart failure and iron deficiency: FERRIC-HF II Randomized Mechanistic Trial. *Circulation*. 2019;139:2386–2398.

KEY WORDS exercise intolerance, female sex, HFpEF, women