Decoding the Diagnostic Dilemmas of Heart Failure with Preserved Ejection Fraction: Applying the Universal Definition for Enhanced Diagnosis Standardization

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Heart Failure (HF) is a clinical syndrome in which the heart is unable to meet the metabolic demands of the body at normal level of filling pressures, whether at rest or while exercising.[1] Traditionally, HF is classified based on the left ventricular ejection fraction (LVEF), which measures the percentage of the left ventricular end diastolic volume ejected during each contraction. Whereas a normal LVEF is established as ≥50%, it is worth noting that approximately half of all HF patients display values within this normal range.

HF with Preserved Ejection Fraction (HFpEF) and HF with Reduced Ejection Fraction (HFrEF) are distinct diseases characterized by different underlying mechanisms, diagnostic workup and treatment approaches.[2] Moreover, diagnosing HFpEF in clinical practice is often more challenging due to the lack of standardized criteria in clinical trials and guidelines,[3,4] as well as complexities arising from the heterogeneity of the HFpEF syndrome.[5] In an attempt to standardize the diagnosis of HF, a universal definition and classification of HF were proposed,[6] encompassing the diverse spectrum of HF phenotypes based on LVEF.

According to this guideline, a diagnosis of HF requires the presence of past or current symptoms and/or signs of HF caused by structural/functional cardiac abnormalities and corroborated by at least one of the following: 1) elevated natriuretic peptides (NP); or 2) objective evidence of cardiogenic pulmonary or systemic congestion.[6]

Nevertheless, how can we apply these universal HF criteria to the unique intricacies of diagnosing HFpEF?

Implementing the Universal Definition of HF for HFpEF Diagnosis

The clinical diagnosis of HFpEF is straightforward when a patient presents with typical symptoms and signs of left and/or right congestive HF with LVEF ≥50%, along with echocardiography abnormalities and elevated NP.

However, patients with HFpEF may not display this classical HF presentation. Indeed, a significant proportion of patients (~50%) will only display symptoms during exertion, without current or previous evidence of fluid overload on clinical examination or prior hospitalization for decompensated HF[7] (Figure 1). This exercise-induced left atrial hypertension phenotype makes diagnosis challenging in clinical practice, with the Framingham criteria showing limited sensitivity.[1,6]

Moreover, some HFpEF patients may lack detectable structural abnormalities in imaging studies. For instance, Ho et al.[3] found that in a cohort of 243 patients with an invasive diagnosis of HFpEF, 59% lacked left atrial enlargement, 73% lacked LV hypertrophy, and 29% had no abnormalities in resting echocardiography. Similarly, functional abnormalities may not be evident, leading to low sensitivity of these features for HFpEF diagnosis.

Elevated NP are commonly observed in patients with HFpEF, as demonstrated in the DELIVER trial, where the median NT-proBNP was 1011 pg/mL.[8] However, it is important to note that patients with HFpEF can definitely display normal NP levels, yet they still face a threefold increase in mortality rates compared to patients without HF.[9]

In such cases, the guideline recommends investigating objective evidence of cardiogenic pulmonary or systemic congestion using diagnostic modalities such as chest radiography or elevated filling pressures on echocardiography, or even invasive hemodynamic measurements (e.g., pulmonary artery catheter) at rest or during exercise.

Echocardiographic Assesment of Diastolic Dysfunction to Diagnose HFpEF

Echocardiography is the main diagnostic tool for evaluating patients suspected of having HFpEF. Nonetheless, what the current evidence-based arguments support the predictive capabilities of echocardiographic parameters and its diastolic indexes in assessing cardiac filling pressures or establishing a formal diagnosis of HFpEF?

In 2016, the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI) jointly updated their recommendations, combining the best evidence with expert opinions, and endorsed the algorithm "B" for assessing filling pressures. Nevertheless, it is worth noting that, despite this endorsement, at least three significant studies showed conflicting results regarding the performance of the ASE 2016 algorithm to predict filling pressures,[10-13] raising concerns about its external validity.

Initially, HFpEF was described as "diastolic HF," but this terminology is no longer recommended. While echocardiography remains as a key diagnostic tool for assessing HFpEF, it is crucial to recognize that diastolic dysfunction observed

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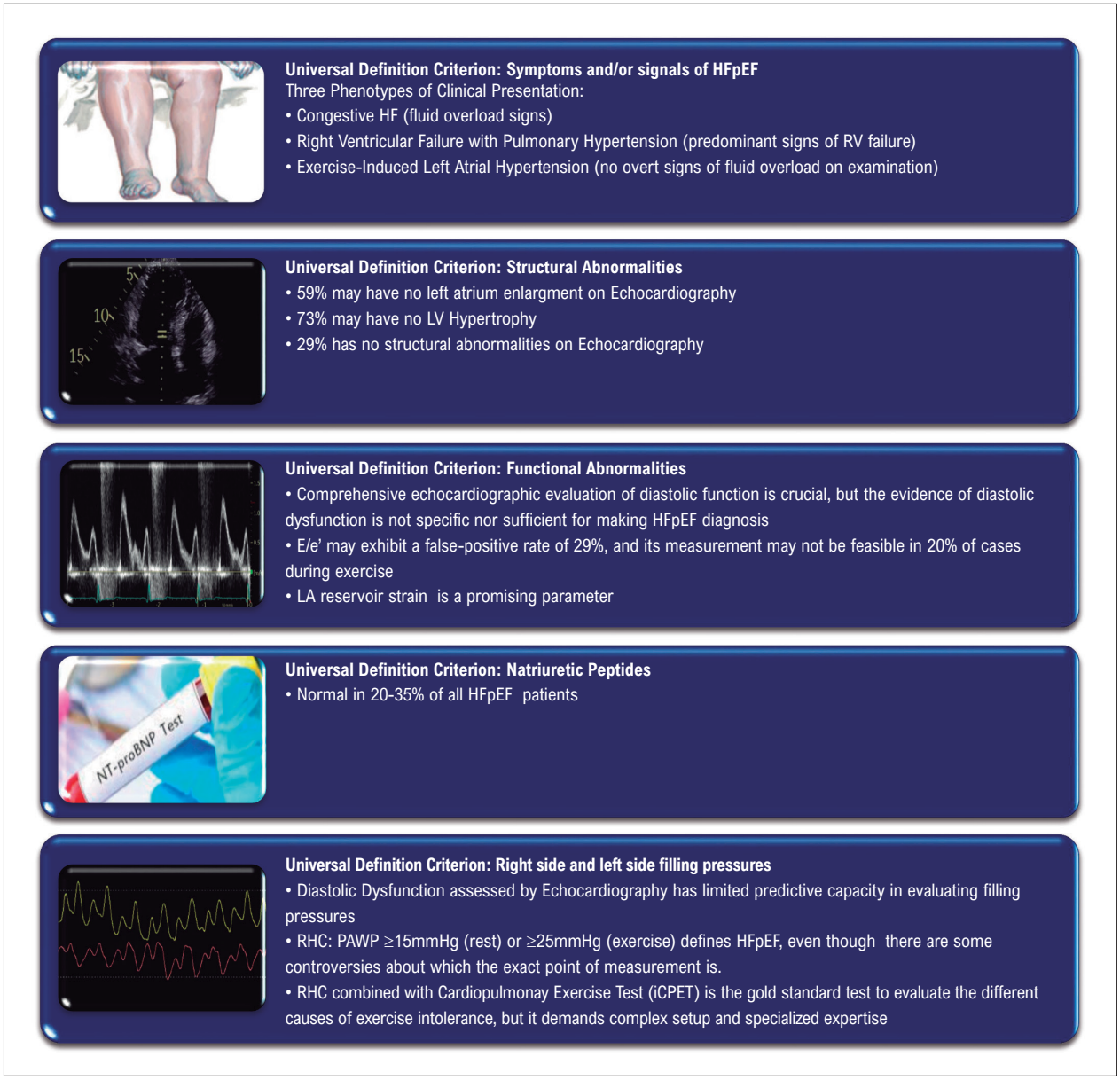

Figure 1 – *Applying the Criteria of Universal Definition of HF for HFpEF diagnosis. HFpEF: HF with Preserved Ejection Fraction; RV: right ventricle; LV: left ventricle; LA: left atrium; RHC: right heart catheterization; PAWP: pulmonary capillary wedge pressure.*

on echocardiography is not specific or sufficient for making an HFpEF diagnosis.[1]

One of the main echocardiography parameters used is the E/e' ratio, which is associated with mean left atrial pressure. Bovenkamp et al.[10] demonstrated that E/e' >9 had sensitivity of 78% and specificity of 59%, whereas a cut of E/e'>14 had lower sensitivity (38%), but higher specificity (89%). However, the reliability of the E/e' ratio may be compromised in various clinical scenarios, including mitral annulus calcification, conduction delay, regional wall motion abnormalities, and high output state.[14,15]

In the diastolic stress test during exercise, the measurement of E/e' may be challenging, with approximately 20% being unfeasible during peak exercise and a false-positive rate at approximately 29%.[16]

Left atrial reservoir strain (LArS) is a promising parameter for HFpEF diagnosis. LArS ≤18% or ≤24% is associated with increased filling pressures.[17] However, this parameter, along with other new parameters derived from speckle tracking[18,19] demand further research to evaluate its performance in less selected populations.

Using the recently proposed H_2FPEF[20] and HFA-PEFF[2] scores for suspected HFpEF can be valuable in balancing clinical, echocardiographic, and NP parameters in the diagnostic workup (Figure 2). The H_2FPEF score, proposed by the Mayo Clinic group in 2018, provides a probability

of HFpEF for individuals with unexplained dyspnea and has been validated using invasive measurements of pulmonary capillary wedge pressure (PAWP). It is important to note that the prevalence of HFpEF in this study population was 64%, which may lead to selection bias.[20]

In 2019, the European Society of Cardiology published a consensus recommendation proposing a stepwise approach to evaluate patients with suspected HFpEF. After excluding other conditions that may mimic HFpEF in the pre-test assessment (Step "P"), they suggested a scoring system (Step "E") to classify patients as having low, intermediate, or high probability of HFpEF.[2] This scoring system was subsequently prospectively validated.[21]

While validation studies generally demonstrate good overall performance for both score systems, some inaccuracies have been identified. For example, false negative rates of 25% (23 out of 91 cases) and 28% (14 out of 50 cases) were reported for patients classified as low probability (score) or 1) by HFAPEFF and H_2FPEF, respectively.[22]

Furthermore, recent data suggest that applying these scores to less selected populations may result in high prevalence of intermediate scores,[23,24] requiring additional tests such as exercise right heart catheterization (RHC).

Exercise RHC for the Diagnosis of HFpEF

Exercise RHC is the gold standard for diagnosing HFpEF as it directly measures PAWP. In reference centers, simultaneous measurement of VO_2 (Invasive CardioPulmonary Test) allows estimation of the kinetics of all components of the Fick equation through the different stages of exercise.

A PAWP ≥15mmHg at rest or ≥25mmHg during exercise defines HFpEF.[25-27] Additionally, the increase in PAWP indexed to change in cardiac output (PAWP slope/Cardiac Output>2) has been proposed as a diagnostic criterion to define HFpEF.[28]

However, conducting RHC requires a complex setup and demands specialized expertise for data acquisition and interpretation. Moreover, there are notable variations in protocols (upright vs. supine) and standardization methods for measuring PAWP, such as the reference point (mid-A wave end of expiration vs. mean during the respiratory cycle).[29]

Despite those limitations, exercise RHC is a highly accurate approach to fulfill the criteria for objective evidence of pulmonary congestion as stipulated by the universal definition of HF. Furthermore, it not only provides insights into the mechanisms underlying exercise limitation, but also enables prognostication of patients diagnosed with HFpEF.

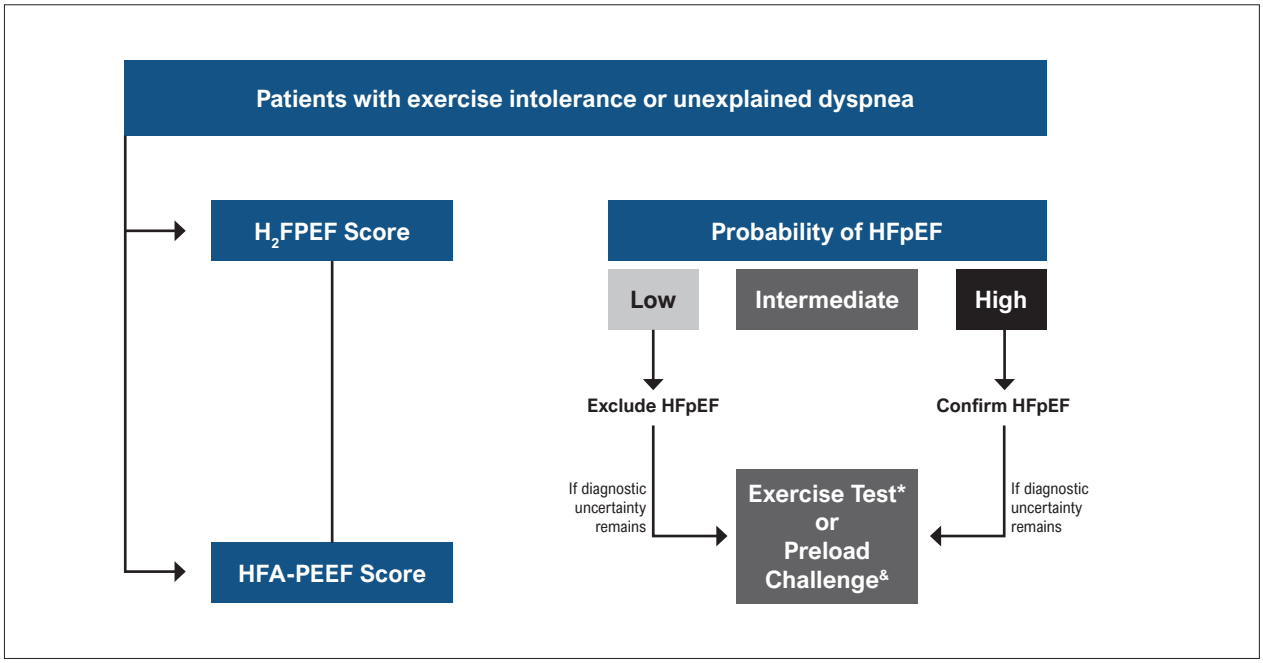

Figure 2 – *Current recommendations for the diagnostic approach of patients with suspected HFpEF. HFpEF: Heart Failure with Preserved Ejection Fraction; *Exercise Test encompasses both Diastolic Stress Echocardiography and Exercise RHC. &Preload Challenge refers either to infusion of normal saline or passive leg raising maneuver during RHC*

References

1. Kittleson MM, Panjrath GS, Amancherla K, Davis LL, Deswal A, Dixon DL, et al. 2023 ACC Expert Consensus Decision Pathway on Management of Heart Failure with Preserved Ejection Fraction: A Report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2023;81(18):1835-78. doi: 10.1016/j.jacc.2023.03.393.

2. Pieske B, Tschöpe C, Boer RA, Fraser AG, Anker SD, Donal E, 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(40):3297-317. doi: 10.1093/eurheartj/ehz641.

3. Ho JE, Zern EK, Wooster L, Bailey CS, Cunningham T, Eisman AS, et al. Differential Clinical Profiles, Exercise Responses, and Outcomes Associated with Existing HFpEF Definitions. Circulation. 2019;140(5):353-65. doi: 10.1161/CIRCULATIONAHA.118.039136.

4. Ho JE, Redfield MM, Lewis GD, Paulus WJ, Lam CSP. Deliberating the Diagnostic Dilemma of Heart Failure with Preserved Ejection Fraction. Circulation. 2020;142(18):1770-80. doi: 10.1161/CIRCULATIONAHA.119.041818.

5. Shah SJ, Borlaug BA, Kitzman DW, McCulloch AD, Blaxall BC, Agarwal R, et al. Research Priorities for Heart Failure with Preserved Ejection Fraction: National Heart, Lung, and Blood Institute Working Group Summary. Circulation. 2020;141(12):1001-26. doi: 10.1161/CIRCULATIONAHA.119.041886.

6. Bozkurt B, Coats AJS, Tsutsui H, Abdelhamid CM, Adamopoulos S, Albert N, et al. Universal Definition and Classification of Heart Failure: A Report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure: Endorsed by the Canadian Heart Failure Society, Heart Failure Association of India, Cardiac Society of Australia and New Zealand, and Chinese Heart Failure Association. Eur J Heart Fail. 2021;23(3):352-80. doi: 10.1002/ejhf.2115.

7. Litwin SE, Komtebedde J, Hu M, Burkhoff D, Hasenfuß G, Borlaug BA, et al. Exercise-Induced Left Atrial Hypertension in Heart Failure with Preserved Ejection Fraction. JACC Heart Fail. 2023:S2213-1779(23)00095-1. doi: 10.1016/j.jchf.2023.01.030.

8. Solomon SD, Vaduganathan M, Claggett BL, Boer RA, DeMets D, Hernandez AF, et al. Baseline Characteristics of Patients with HF with Mildly Reduced and Preserved Ejection Fraction: DELIVER Trial. JACC Heart Fail. 2022;10(3):184-97. doi: 10.1016/j.jchf.2021.11.006.

9. Verbrugge FH, Omote K, Reddy YNV, Sorimachi H, Obokata M, Borlaug BA. Heart failure with Preserved Ejection Fraction in Patients with Normal Natriuretic Peptide Levels is Associated with Increased Morbidity and Mortality. Eur Heart J. 2022;43(20):1941-51. doi: 10.1093/eurheartj/ehab911.

10. van de Bovenkamp AA, Enait V, Man FS, Oosterveer FTP, Bogaard HJ, Vonk Noordegraaf A, et al. Validation of the 2016 ASE/EACVI Guideline for Diastolic Dysfunction in Patients With Unexplained Dyspnea and a Preserved Left Ventricular Ejection Fraction. J Am Heart Assoc. 2021;10(18):e021165. doi: 10.1161/JAHA.121.021165.

11. Gillebert TC. Estimating LV Filling Pressures Noninvasively: A Word of Caution. JACC Cardiovasc Imaging. 2022;15(10):1692-5. doi: 10.1016/j.jcmg.2022.05.003.

12. Andersen OS, Smiseth OA, Dokainish H, Abudiab MM, Schutt RC, Kumar A, et al. Estimating Left Ventricular Filling Pressure by Echocardiography. J Am Coll Cardiol. 2017;69(15):1937-48. doi: 10.1016/j.jacc.2017.01.058.

13. Pak M, Kitai T, Kobori A, Sasaki Y, Okada T, Murai R, et al. Diagnostic Accuracy of the 2016 Guideline-Based Echocardiographic Algorithm to Estimate Invasively-Measured Left Atrial Pressure by Direct Atrial Cannulation. JACC Cardiovasc Imaging. 2022;15(10):1683-91. doi: 10.1016/j.jcmg.2022.03.022.

14. Oh JK, Miranda WR, Kane GC. Diagnosis of Heart Failure with Preserved Ejection Fraction Relies on Detection of Increased Diastolic Filling Pressure, But How? J Am Heart Assoc. 2023;12(6):e028867. doi: 10.1161/JAHA.122.028867.

15. Hortegal R AH. Ecocardiografia com Strain para Avaliação de Pacientes com Disfunção Diastólica e Fração de Ejeção Preservada: Estamos Prontos? Arq Bras Cardiol: Imagem Cardiovasc. 2017;30(4):132-9. doi: 10.5935/2318-8219.20170034 .

16. Obokata M, Kane GC, Reddy YN, Olson TP, Melenovsky V, Borlaug BA. Role of Diastolic Stress Testing in the Evaluation for Heart Failure with Preserved Ejection Fraction: A Simultaneous Invasive-Echocardiographic Study. Circulation. 2017;135(9):825-38. doi: 10.1161/CIRCULATIONAHA.116.024822.

17. Inoue K, Khan FH, Remme EW, Ohte N, García-Izquierdo E, Chetrit M, et al. Determinants of Left Atrial Reservoir and Pump Strain and Use of Atrial Strain for Evaluation of Left Ventricular Filling Pressure. Eur Heart J Cardiovasc Imaging. 2021;23(1):61-70. doi: 10.1093/ehjci/jeaa415.

18. Hortegal RA, Hossri C, Giolo L, Cancellier R, Gun C, Assef J, et al. Mechanical Dispersion is a Superior Echocardiographic Feature to Predict Exercise Capacity in Preclinical and Overt Heart Failure with Preserved Ejection Fraction. Int J Cardiovasc Imaging. 2023;39(7):1239-50. doi: 10.1007/s10554-023-02830-0.

19. Hortegal RA, Valeri R, Grizante M, Cancellier R, Uemoto V, Gun C, et al. Afterload Increase Challenge Unmasks Systolic Abnormalities in Heart Failure with Preserved Ejection Fraction. Int J Cardiol. 2023;380:20-7. doi: 10.1016/j.ijcard.2023.03.042.

20. Reddy YNV, Carter RE, Obokata M, Redfield MM, Borlaug BA. A Simple, Evidence-Based Approach to Help Guide Diagnosis of Heart Failure with Preserved Ejection Fraction. Circulation. 2018;138(9):861-70. doi: 10.1161/CIRCULATIONAHA.118.034646.

21. Aizpurua AB, Wijk SS, Rocca HPB, Henkens M, Heymans S, Beussink-Nelson L, et al. Validation of the HFA-PEFF Score for the Diagnosis of Heart Failure with Preserved Ejection Fraction. Eur J Heart Fail. 2020;22(3):413-21. doi: 10.1002/ejhf.1614.

22. Churchill TW, Li SX, Curreri L, Zern EK, Lau ES, Liu EE, et al. Evaluation of 2 Existing Diagnostic Scores for Heart Failure with Preserved Ejection Fraction Against a Comprehensively Phenotyped Cohort. Circulation. 2021;143(3):289-91. doi: 10.1161/CIRCULATIONAHA.120.050757.

23. Tada A, Nagai T, Omote K, Iwano H, Tsujinaga S, Kamiya K, et al. Performance of the H2FPEF and the HFA-PEFF Scores for the Diagnosis of Heart Failure with Preserved Ejection Fraction in Japanese Patients: A Report from the Japanese Multicenter Registry. Int J Cardiol. 2021;342:43-8. doi: 10.1016/j.ijcard.2021.08.001.

24. Amanai S, Harada T, Kagami K, Yoshida K, Kato T, Wada N, et al. The H2FPEF and HFA-PEFF Algorithms for Predicting Exercise Intolerance and Abnormal Hemodynamics in Heart Failure with Preserved Ejection Fraction. Sci Rep. 2022;12(1):13. doi: 10.1038/s41598-021-03974-6.

25. Hsu S, Fang JC, Borlaug BA. Hemodynamics for the Heart Failure Clinician: A State-of-the-Art Review. J Card Fail. 2022;28(1):133-48. doi: 10.1016/j.cardfail.2021.07.012.

26. Borlaug BA, Nishimura RA, Sorajja P, Lam CS, Redfield MM. Exercise Hemodynamics Enhance Diagnosis of Early Heart Failure with Preserved Ejection Fraction. Circ Heart Fail. 2010;3(5):588-95. doi: 10.1161/CIRCHEARTFAILURE.109.930701.

27. Deis T, Wolsk E, Mujkanovic J, Komtebedde J, Burkhoff D, Kaye D, et al. Resting and Exercise Haemodynamic Characteristics of Patients with Advanced Heart Failure and Preserved Ejection Fraction. ESC Heart Fail. 2022;9(1):186-95. doi: 10.1002/ehf2.13697.

28. Eisman AS, Shah RV, Dhakal BP, Pappagianopoulos PP, Wooster L, Bailey C, et al. Pulmonary Capillary Wedge Pressure Patterns During Exercise Predict Exercise Capacity and Incident Heart Failure. Circ Heart Fail. 2018;11(5):e004750. doi: 10.1161/CIRCHEARTFAILURE.117.004750.

29. Pagnamenta A, Azzola A, Beghetti M, Lador F, On Behalf Of The Swiss Society Of Pulmonary Hypertension. Invasive Haemodynamic Evaluation of the Pulmonary Circulation in Pulmonary Hypertension. Swiss Med Wkly. 2017;147:w14445. doi: 10.4414/smw.2017.14445.