Cardiology Journal

VIA MEDICA

ORIGINAL ARTICLE

DOI: 10.5603/cj.95191

ISSN 1897–5593
eISSN 1898–018X

Heart failure with preserved ejection fraction: diagnostic value of HFA-PEFF score, H_2FPEF score, and the diastolic stress echocardiography

Andrzej Kubicius[1], Zbigniew Gąsior[2], Maciej Haberka[2]

[1]Department of Cardiology in Cieszyn, Upper Silesia Medical Center, Medical University of Silesia, Katowice, Poland

[2]Department of Cardiology, SHS, Medical University of Silesia, Katowice, Poland

Abstract

Introduction: *The aim of our study was to compare 3 diagnostic pathways: diastolic stress echocardiography (DSE) based on the ASE/EACVI 2016 guidelines, the 2018 H_2FPEF score, and the 2019 HFA-PEFF algorithm, in patients suspected of heart failure with preserved ejection fraction (HFpEF).*

Material and methods: *The study group included 80 consecutive patients with a clinical suspicion of HFpEF. The H_2FPEF and HFA-PEFF scores and serum NT-proBNP concentrations were assessed in all the patients before they were sent for DSE.*

Results: *The DSE-based pathway confirmed HFpEF in 17 (21%) patients, the HFA-PEFF algorithm in 43 (54%), and H_2FPEF scoring in 4 (5%) patients. The ROC analysis showed that HFA-PEFF score > 5 predicts a DSE-positive test with a sensitivity of 70.5% and a specificity of 65%, (AUC = 0.711, p = 0.002) with a negative predictive value of 89.1% and positive predictive value of 35.3%. The H_2FPEF score > 3 had a negative predictive value of 90%, a positive predictive value of 29.8%, and predicted positive DSE result with a sensitivity of 82.3% but rather poor specificity of 47.6% (AUC = 0.692, p = 0.004). Both H_2FPEF and HFA-PEFF showed similar predictive values (AUC) in the prediction of positive DSE test (p = ns).*

Conclusions: *The HFA-PEFF score overestimated the rate of HFpEF in comparison to DSE and the H_2FPEF score. The H_2FPEF and HFA-PEFF scores showed only modest predictive values of the positive DSE and had a diagnostic power to rule out the HFpEF.*

Keywords: diastolic stress echocardiography, H_2FPEF, HFA-PEFF, HFpEF

Introduction

Heart failure with preserved ejection fraction of the left ventricle (HFpEF) is diagnosed in more than 50% of subjects with heart failure, and its prevalence has been growing in recent years [1, 2]. The major risk factors for HFpEF are age, diabetes, hypertension, and coronary heart disease. There is a difference in the prevalence between HFpEF and heart failure (HF) with reduced ejection fraction (HFrEF) increasing with the patient's age. In western countries, it has become a predominant type of HF in the population over 65 years old, accounting for more than 70% of individuals [3, 4].

So far, there has been poor evidence for the benefit of pharmacological treatment in reducing morbidity, mortality, and HF hospitalizations in those patients. [5] However, the results of recent studies with sodium-glucose cotransporter-2 (SGLT2) inhibitors are very promising [6, 7].

Address for correspondence: Andrzej Kubicius, Department of Cardiology in Cieszyn, Medical University of Silesia, Bielska 4 St., 43-400 Cieszyn; tel.: +48 505054641; e-mail: a.kub@interia.pl

Received: 23.04.2023 Accepted: 23.12.2023 Early publication date: 08.04.2024

There is still a great need for a simple algorithm to establish a diagnosis of HFpEF and define the group of patients who would benefit from the appropriate treatment. Therefore, there are several diagnostic definitions and algorithms for HFpEF provided in various papers [8–11]. It reflects their limitations and may affect the proper diagnosis. Heterogeneity of echocardiographic parameters and clinical characteristics within study groups depending on the age, body mass index (BMI), heart rhythm, kidney function, and comorbidities determine the lack of single parameters with a clear cut-off value for HFpEF diagnosis [12]. The ASE/EACVI 2016 guidelines for diastolic dysfunction (DD) diagnosis and left atrial pressure (LAP) assessment include relatively simple parameters. However, there are still a lot of patients with indication for stress echocardiography (SE) due to indeterminate conclusion of transthoracic echocardiography (TTE) [10].

Reddy et al. provided the H_2FPEF score based on a cohort of patients with dyspnea and preserved LVEF scheduled for exercise invasive right heart catheterization (RHC) [13]. The HFA-PEFF algorithm is another stepwise approach provided by Pieske et al. [11]. However, both algorithms may provide different conclusions in the same individuals [12].

The aim of our study was to compare 3 diagnostic pathways in patients with a suspected HFpEF. The secondary aim was to assess the predictive values of HFA-PEFF and H_2PEF scores towards the positive DSE test.

Material and methods

The study group included 80 consecutive patients referred to diastolic stress echocardiography (DSE) due to a suspicion of HFpEF based on clinical symptoms and TTE according to ASE/EACVI guidelines [10].

The exclusion criteria were as follows: systolic dysfunction defined as LVEF < 50%, severe DD considered as restrictive filling pattern in TTE at rest, significant valve disease (at least moderate-to-severe regurgitations and at least mild valvular stenosis), atrial fibrillation during evaluation, severe chronic kidney disease (GFR < 30 ml/min × 1.73 m^2), acute cardiovascular diseases in the prior 8 weeks (e.g., acute coronary syndrome, acute pulmonary embolism, stroke), and significant chronic pulmonary diseases and acute infectious disease in the prior 4 weeks.

A routine TTE focused on DD evaluation according to the ASE guidelines [10, 14] was performed in all subjects at enrollment. The following parameters were assessed: average E/e' > 14, septal e' velocity < 7 cm/s or lateral e' velocity < 10 cm/s, TR velocity > 2.8 m/s, and LA volume index > 34 ml/m^2. If more than 50% were positive, the DD was confirmed. Otherwise, the DD was found to be indeterminate (50% of abnormal parameters) or normal (< 50%).

Afterwards, all the subjects were scheduled for SE using a treadmill ergometer (Aspel, Cardiotest B612, Poland) limited by symptoms and fatigue, according to the ASE clinical recommendation [15]. TTE was performed at rest and just after the exercise. The image acquisitions were started within the first minute of the rest. DSE test was considered positive when the following conditions were met: average E/e' > 14 and peak TR velocity > 2.8 m/s [10].

The Philips HD15 ultrasound system (USA, Bothel, WA 98021) was used in all cases, and anonymized echocardiographic data were stored digitally. All the DSE tests were performed by one operator and analyzed offline blinded to the lab tests results.

The blood samples were collected in all the study patients to assess serum NTproBNP concentrations (BioVendro R&D, Cz).

HFpEF diagnostic pathways

There were 3 diagnostic pathways used in the study group: DSE based on ASE/EACVI 2016 guidelines, the 2018 H2FPEF score, and the 2019 HFA-PEFF algorithm [10, 11, 13].

According to the H2FPEF score, the following clinical and echocardiographic data were obtained: BMI > 30 kg/m2 — 2 points, hypertension treated with at least 2 antihypertensive medicines — 1 point, history of paroxysmal or persistent atrial fibrillation — 3 points, systolic pulmonary artery pressure (sPAP) > 35 mmHg, assessed from Doppler echocardiography — 1 point, age > 60 years — 1 point, and E/e' ratio > 9 — 1 point. A total score of 0 –1 points was considered as unlikely for HFpEF determination, while score of 5–6 points were considered as positive for HFpEF diagnosis, and an intermediate score of 2–4 points were considered as a requirement for further evaluation [13].

The HFA-PEFF score assessment required the following parameters:

— functional major: for age < 75 years: septal e' < 7 cm/s or lateral e' < 10 cm/s, for age < 75 years: septal e' < 7 cm/s or lateral e' < 10 cm/s, average E/e' ≥ 15; TRV > 2.8 m/s (sPAP > 35 mmHg),

— functional minor: average E/e' 9–14,
— morphological major: LAVI > 34 ml/m² or RWT > 0.42 and LVMI: men ≥ 149 g/m² women ≥ 122 g/m²,
— morphological minor: LAVI 29–34 ml/m² or RWT > 0.42 or LVMI: men: 116–149 g/m², women: 96–122 g/m² or LV wall thickness ≥ 12 mm,
— biomarker major: NT — pro BNP: > 220 pg/ml and minor: NT — pro BNP: 125–220 pg/ml.

The final score was obtained by adding 2 points for one major criterion from each domain or one point for minor criterion, respectively. We did not use the global longitudinal strain criterion because it was not evaluated in the study. All the patients with atrial fibrillation at the time of enrollment were excluded from the study. The likelihood of HFpEF diagnosis was assessed as low with total score of 0–1 points, intermediate with 2–4 points, and high with 5–6 points.

The study was conducted in accordance with the principles of the Declaration of Helsinki and the Local Ethics Committee. The study was approved by the Ethics Committee of the Medical University of Silesia in Katowice. This work was supported by a non-commercial research grant from the Medical University of Silesia (PCN-1-102/N/1/Z).

Statistical analysis

Qualitative parameters are presented as numbers and percentages. Distributions of continuous variables were analyzed using the Kolmogorov-Smirnov test. All the continuous variables that are normally distributed are presented as means and standard deviations (SD) and non-normally distributed as medians and interquartile ranges. Student's t-test, the Mann-Whitney U test, and the χ^2 test were used where appropriate to test the differences among parameters and between groups. To determine the best cut-off of baseline parameters, the receiver operating characteristic (ROC) curves were used providing sensitivity, specificity, and optimal predictive values for diastolic dysfunction. A p value < 0.05 was considered statistically significant. Statistical analysis was performed using MedCalc software (version 19.1).

Results

The study group included 80 patients (mean [SD] age: 69 [8]; 25% males) with dyspnea (NYHA II — 70; III — 10) and the following risk factors: hypertension (96%), obesity (56%), diabetes (41%), coronary artery disease (10%), chronic kidney disease (26%), and history of atrial fibrillation (7.5%) (Table 1).

Table 1. Clinical characteristics of the study group.

Age, years, mean (SD)	69 (8.1)
Males, n (%)	20 (25)
BMI, kg/m², mean, (SD)	31 (4.9)
normal weight/overweight, n, (%)	5 (6.2)/30 (37.5)
class I obesity, n, (%)	24 (30)
class II obesity, n, (%)	17 (21.3)
class III obesity, n, (%)	4 (5)
HR, (SD)	74.2 (10.4)
SBP/DBP, (SD)	131.2 (15.8)/77 (8.4)
NYHA class	
II, n, (%)	70 (87.5)
III, n, (%)	10 (12.5)
Medical history	
coronary disease, n, (%)	8 (10)
hypertension, n, (%)	77 (96)
diabetes, n, (%)	33 (41.3)
chronic kidney disease, n, (%)	22 (27.5)
history of atrial fibrillation, n, (%)	6 (7.5)
current smoker, n, (%)	5 (6.3)
Medication	
Beta-blockers, n, (%)	70 (87.5)
ACE-I or ARB, n, (%)	67 (83.8)
Aldosterone antagonists, n, (%)	5 (6.3)
Diuretics, n, (%)	34 (42.5)
Calcium antagonists, n, (%)	37 (46.3)
Antidiabetic drugs/ Insulin, n, (%)	17 (21.3)/8 (10)
Statins, n, (%)	60 (75)

The DSE-based pathway confirmed HFpEF in 17 (21%) patients. The HFA-PEFF algorithm including NT-proBNP concentration showed a high HFpEF probability in 43 (54%) patients, and while using H_2FPEF scoring only 4 (5%) patients from the study group met the criteria of HFpEF high likelihood (Figure 1).

The intermediate probability of HFpEF was found in 37 patients (46%) according to the HFA-PEFF score and 70 patients (87%) according to the H2FPEF score. The diagnosis of HFpEF was ruled out in 6 patients (7%) according to H_2FPEF algorithm.

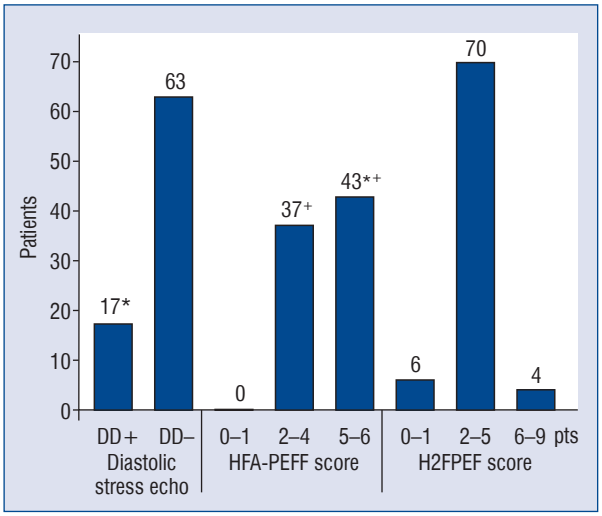

Figure 1. The DSE, HFA-PEFF and H2FPEF scores in the study group; *p < 0.0001; +p = 0.31.

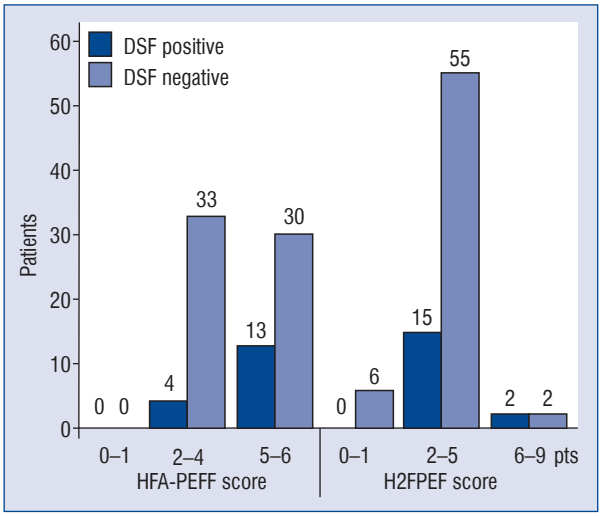

Figure 2. The H_2FPEF and HFA-PEFF scores and the DSE test result.

Table 2. NT-proBNP concentrations according to DSE and HFA-PEF score result.

Variable	NTproBNP (pg/ml), median (IQR)		p-value
DSE	DD (+) n = 17 443.8 (316.2–781.2)	DD (–) n = 63 240.9 (142.1–438.7)	p = 0.007
HFA-PEFF Score	5–6 points, n = 43 440.1 (266.1–620.2)	3–4 points, n = 37 160.2 (82.2–225.1)	p < 0.0001

DSE — diastolic stress echocardiography; DD — diastolic dysfunction; NT-proBNP — n-terminal pro B-type natriuretic peptide.

The prevalence of positive DSE test results in the group of intermediate HFpEF probability according to the HFA-PEFF and H_2FPEF approach was 11% (4 out of 37) and 21% (15 out of 70), respectively. Finally, a positive DSE test was found in 30% (13 out of 43) of patients with a high HFpEF probability (HFA- PEFF) and 50% (2 out of 4) of individuals assessed in H_2FPEF score (Figure 2).

There was a significant difference in NT-proBNP concentrations between groups with positive and negative DSE test result and moderate or high HFpEF probability assessed with HFA-PEFF score (Table 2).

We found a significant difference in echocardiographic DD parameters both in rest and stress between groups with a high HFpEF probability (HFA-PEFF score of 5–6) and a borderline probability (HFA-EFF score of 4–5). The results are shown in Table 3.

Most of the study patients (70) were found to have an H_2FPEF score between 2 and 5 points. Therefore, the H_2FPEF score was not included in the analysis of NT-proBNP or echocardiographic parameters.

The ROC analysis showed that HFA-PEFF score > 5 predicted a positive DSE test with a sensitivity of 70.5% and a specificity of 65%, (AUC = 0.711, p = 0.002) with a high negative predictive value of 89.1% and a relatively low positive predictive value of 35.3%.

However, H_2FPEF score > 3 had a very high negative predictive value of 90%, a positive predictive value of 29.8%, and predicted positive DSE test result with a high sensitivity of 82.3% but rather poor specificity of 47.6% (AUC = 0.692, p = 0.004).

Both H_2FPEF and HFA-PEFF showed similar predictive values (AUC) in the prediction of positive DSE test (p = ns) (Figure 3).

Discussion

Our study showed that different algorithms of HFpEF diagnosis may give divergent results. A considerable number of patients within the indeterminate group assessed with ASE/EACVI and H_2FPEF algorithm had a high probability of HFpEF using the HFA-PEFF score. The HFA-PEFF

Table 3. Echocardiographic parameters and HFA-PEFF scores.

Variable	HFA PEFF score 5–6 (n = 43)	HFA PEFF score 4–5 (n = 34)	Difference (95% CI)	p-value
E/e' mean rest mean (SD)	13.0 (4.4)	10.1 (2.6)	–2.9 (–4.6 to –1.2)	0.001
E/e' mean stress mean (SD)	15.6 (4.4)	12.3 (3.2)	–3.3 (–5.1 to –1.5)	0.0004
LA volume index rest (ml/m²) mean (SD)	41.5 (7.8)	30.2 (6.8)	–11.3 (–14.6 to –7.9)	< 0.0001
LA volume index stress (ml/m²) mean (SD)	37.6 (9.0)	32.5 (9.0)	–5.0 (–9.1 to –0.9)	0.0176
TRPG rest (mmHg) mean (SD)	18.5 (17.7)	10.7 (14.8)	–7.8 (–15.4 to –0.3)	0.0423

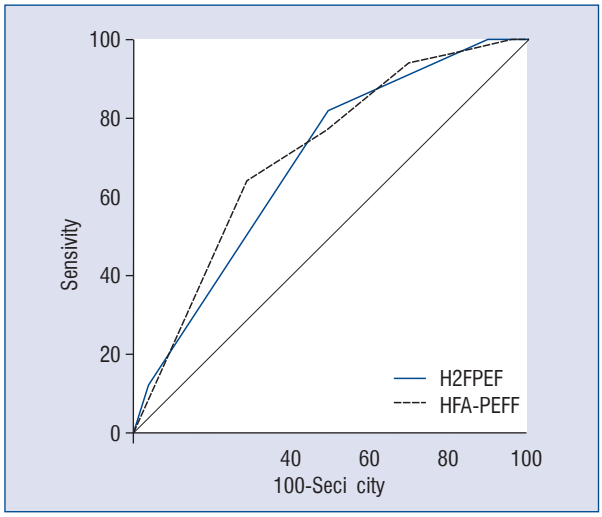

Figure 3. ROC analysis: comparison of H2FPEF and HFA-PEFF predictive values (p = ns)

score provides the highest rate and the H_2FPEF provides the lowest rate of HFpEF patients in the same group.

Both H_2FPEF and HFA-PEFF algorithms have high negative predictive values towards a positive DSE test result, but their positive predictive power is rather poor. Moreover, we found that DSE and HFA-PEFF conclusions are concordant with NT-proBNP concentrations.

We showed that both HFA-PEFF and H_2PEF have rather moderate accuracy in the prediction of a definite HFpEF diagnosis with a positive DSE. The study of Amanai S. et al. was designed to compare H_2FPEF and HFA-PEFF scores in the prediction of reduced aerobic capacity and to assess a correlation between both scores with echocardiographic measurements. While the H_2FPEF score was found to predict a reduced aerobic capacity (AUC 0.71, p = 0.0005), the HFA-PEFF score failed to show a predictive value [16].

Both algorithms have their strengths and limitations, which may result in different scores obtained in the same patient [12]. There is still a need for further evaluation of their clinical values and even some modifications [17]. However, their predictive value for cardiac mortality and cardiac-related events is shown in HFpEF patients [18–20].

NT-proBNP serum concentrations are associated with DD, symptoms, and long-term outcomes [21–23]. It was also noted that NT-proBNP levels are increased in patients with increased exercise filling pressures and exertional dyspnea [24]. However, Anjan et al. showed normal BNP levels in 29% of symptomatic outpatients with HFpEF who had elevated pulmonary capillary wedge pressures. Finally, it was concluded that although BNP was useful as a prognostic marker in HFpEF, normal BNP did not exclude the outpatient diagnosis of HFpEF [25]. There is also the paradox of relatively low NT-proBNP levels in HFpEF patients with obesity [26].

In the general population, atrial remodeling assessed with LAVI is closely associated with the severity of DD, which is most predictive of future death [27]. Among patients without atrial fibrillation or heart valve disease, LAVI > 34 mL/m^2 independently predicted death, heart failure, AF, and ischaemic stroke [28, 29]. The range of LAVI within 29–34 mL/m^2 is considered as a minor criterion because it represents the upper limit in healthy subjects [11]. Similarly abnormal values of relative wall thickness > 0.42 , left ventricle hypertrophy, and LV wall thickness ≥ 12 mm are scored with one point, although their direct correlation

with LVFP is not evident. This may cause lower HFA-PEFF algorithm specificity in some aspects. The H_2FPEF model was derived from the results of retrospective analysis of patients undergoing invasive exercise testing for the evaluation of unexplained dyspnea and validated in a test cohort with robust performance (AUC 0.886) [13].

The HFA-PEFF score is a systematic approach based on the experts' consensus, which was validated mostly with the noninvasive parameters [30]. That is why its "overoptimistic" results were questioned in the review by Kristensen et al. [31]. In the study assessing the HFA-PEFF score against invasive hemodynamic parameters, a moderate predictive value (AUC = 0.73) was found. In the same study, 60% of individuals with intermediate and 91% of patients with high H_2FPEF scores met HFpEF invasive criteria. The cut-off point of ≥ 5 showed a sensitivity and specificity of 31% and 92%, and the positive and negative predictive values were 81% and 55%, respectively, with a moderate AUC of 0.74 [32]. Reddy et al. showed that the H_2FPEF score had a significantly greater predictive value for PCWP/cardiac output ratio compared with the HFA-PEFF score [33].

There is a great deal of evidence that DSE may unmask DD in a considerable number of patients with exertional symptoms [17, 34–36]. The expected individual cardiac output can be achieved only at the expense of increased LV filling pressures [37]. The TTE parameters were poorly sensitive, identifying only 34% to 60% of subjects with an invasively proven HFpEF. The DSE parameters improved the sensitivity (to 90%) and thus the negative predictive value [38]. Therefore, DSE should be recommended in patients with an indeterminate TTE assessment [10] and with an intermediate HFpEF probability according to the H_2FPEF or HFA PEFF scores [11, 13].

There is a large diversity of results depending on the clinical characteristics of the study groups and the adopted criteria for evaluating test results [39, 40]. The prevalence of positive results of DSE ranged from a few percent [41] to almost half of the study group [42]. In our study, there were no subjects with a positive DSE in a low-probability group according to both H_2PEF and HFA-PEFF algorithms. It confirms the high diagnostic value of the clinical scores in ruling out the HFpEF diagnosis [30].

Recent studies provide evidence that LV and LA strain measurements have good correlation with LV filling pressures and diastolic dysfunction degree [43, 44]. Strain assessment would improve DSE accuracy. We did not apply this method, which we consider a limitation of our study.

Conclusions

The HFA-PEFF score overestimated the number of patients with HFpEF in comparison to similar results obtained with DSE and the H_2FPEF score. The H_2FPEF and HFA-PEFF scores showed only modest predictive values of positive DSE. However, both algorithms were found to have diagnostic power to rule out HFpEF.

Acknowledgments: This work was supported by a research non-commercial grant from the Medical University of Silesia (PCN-1-102/N/1/Z).

Statement of competing interests: All authors listed have contributed sufficiently to the project to be included as authors, and all those who are qualified to be authors are listed in the author byline. To the best of our knowledge, no conflict of interest, financial or otherwise, exists. We have included acknowledgements and funding sources after the discussion.

References:

1. Owan TE, Hodge DO, Herges RM, et al. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med. 2006; 355(3): 251–259, doi: 10.1056/NEJMoa052256, indexed in Pubmed: 16855265.
2. Pfeffer MA, Shah AM, Borlaug BA. Heart Failure With Preserved Ejection Fraction In Perspective. Circ Res. 2019; 124(11): 1598–1617, doi: 10.1161/CIRCRESAHA.119.313572, indexed in Pubmed: 31120821.
3. Borlaug BA. Evaluation and management of heart failure with preserved ejection fraction. Nat Rev Cardiol. 2020; 17(9): 559–573, doi: 10.1038/s41569-020-0363-2, indexed in Pubmed: 32231333.
4. Hoffman P. How to diagnose? How to treat? Dilemmas of the HFpEF. Cardiol J. 2020; 27(5): 469–471, doi: 10.5603/CJ.2020.0149, indexed in Pubmed: 33165893.
5. McDonagh TA, Metra M, Adamo M, et al. ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021; 42(36): 3599–3726, doi: 10.1093/eurheartj/ehab368, indexed in Pubmed: 34447992.
6. Packer M, Butler J, Zannad F, et al. Effect of Empagliflozin on Worsening Heart Failure Events in Patients With Heart Failure and Preserved Ejection Fraction: EMPEROR-Preserved Trial. Circulation. 2021; 144(16): 1284–1294, doi: 10.1161/CIRCULATIONAHA.121.056824, indexed in Pubmed: 34459213.
7. Solomon SD, McMurray JJV, Claggett B, et al. DELIVER Trial Committees and Investigators. Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. N Engl J Med. 2022; 387(12): 1089–1098, doi: 10.1056/NEJMoa2206286, indexed in Pubmed: 36027570.

8. Ponikowski P, Voors AA, Anker SD, et al. ESC Scientific Document Group. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016; 37(27): 2129–2200, doi: 10.1093/eurheartj/ehw128, indexed in Pubmed: 27206819.
9. Yancy CW, Jessup M, Bozkurt B, et al. WRITING COMMITTEE MEMBERS, American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 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(16): e240–e327, doi: 10.1161/CIR.0b013e31829e8776, indexed in Pubmed: 23741058.
10. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2016; 29(4): 277–314, doi: 10.1016/j.echo.2016.01.011, indexed in Pubmed: 27037982.
11. 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(40): 3297–3317, doi: 10.1093/eurheartj/ehz641, indexed in Pubmed: 31504452.
12. Kapłon-Cieślicka A, Kupczyńska K, Dobrowolski P, et al. On the search for the right definition of heart failure with preserved ejection fraction. Cardiol J. 2020; 27(5): 449–468, doi: 10.5603/CJ.a2020.0124, indexed in Pubmed: 32986238.
13. Reddy YNV, Carter RE, Obokata M, et al. A Simple, Evidence-Based Approach to Help Guide Diagnosis of Heart Failure With Preserved Ejection Fraction. Circulation. 2018; 138(9): 861–870, doi: 10.1161/CIRCULATIONAHA.118.034646, indexed in Pubmed: 29792299.
14. Mitchell C, Rahko PS, Blauwet LA, et al. Guidelines for Performing a Comprehensive Transthoracic Echocardiographic Examination in Adults: Recommendations from the American Society of Echocardiography. J Am Soc Echocardiogr. 2019; 32(1): 1–64, doi: 10.1016/j.echo.2018.06.004, indexed in Pubmed: 30282592.
15. Pellikka PA, Arruda-Olson A, Chaudhry FA, et al. Guidelines for Performance, Interpretation, and Application of Stress Echocardiography in Ischemic Heart Disease: From the American Society of Echocardiography. J Am Soc Echocardiogr. 2020; 33(1): 1–41.e8, doi: 10.1016/j.echo.2019.07.001, indexed in Pubmed: 31740370.
16. Amanai S, Harada T, Kagami K, et al. The HFPEF 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, indexed in Pubmed: 34996984.
17. Nagueh SF. Diastology: 2020-A practical guide. Echocardiography. 2020; 37(11): 1919–1925, doi: 10.1111/echo.14742, indexed in Pubmed: 32476157.
18. Sueta D, Yamamoto E, Nishihara T, et al. H2FPEF Score as a Prognostic Value in HFpEF Patients. Am J Hypertens. 2019; 32(11): 1082–1090, doi: 10.1093/ajh/hpz108, indexed in Pubmed: 31271191.
19. Hwang IC, Cho GY, Choi HM, et al. H2FPEF Score Reflects the Left Atrial Strain and Predicts Prognosis in Patients With Heart Failure With Preserved Ejection Fraction. J Card Fail. 2021; 27(2): 198–207, doi: 10.1016/j.cardfail.2020.09.474, indexed in Pubmed: 33035685.
20. Sun Y, Si J, Li J, et al. Predictive Value of HFA-PEFF Score in Patients With Heart Failure With Preserved Ejection Fraction. Front Cardiovasc Med. 2021; 8: 656536, doi: 10.3389/fcvm.2021.656536, indexed in Pubmed: 34778384.
21. Gaggin HK, Januzzi JL. Biomarkers and diagnostics in heart failure. Biochim Biophys Acta. 2013; 1832(12): 2442–2450, doi: 10.1016/j.bbadis.2012.12.014, indexed in Pubmed: 23313577.
22. Islam MN, Chowdhury MS, Paul GK, et al. Association of Diastolic Dysfunction with N-terminal Pro-B-type Natriuretic Peptide Level in Heart Failure Patients with Preserved Ejection Fraction. Mymensingh Med J. 2019; 28(2): 333–346, indexed in Pubmed: 31086148.
23. Grewal J, McKelvie R, Lonn E, et al. BNP and NT-proBNP predict echocardiographic severity of diastolic dysfunction. Eur J Heart Fail. 2008; 10(3): 252–259, doi: 10.1016/j.ejheart.2008.01.017, indexed in Pubmed: 18331967.
24. Tschöpe C, Kasner M, Westermann D, et al. Elevated NT-ProBNP levels in patients with increased left ventricular filling pressure during exercise despite preserved systolic function. J Card Fail. 2005; 11(5 Suppl): S28–S33, doi: 10.1016/j.cardfail.2005.04.013, indexed in Pubmed: 15948097.
25. Anjan VY, Loftus TM, Burke MA, et al. Prevalence, clinical phenotype, and outcomes associated with normal B-type natriuretic peptide levels in heart failure with preserved ejection fraction. Am J Cardiol. 2012; 110(6): 870–876, doi: 10.1016/j.amjcard.2012.05.014, indexed in Pubmed: 22681864.
26. Buckley LF, Canada JM, Del Buono MG, et al. Low NT-proBNP levels in overweight and obese patients do not rule out a diagnosis of heart failure with preserved ejection fraction. ESC Heart Fail. 2018; 5(2): 372–378, doi: 10.1002/ehf2.12235, indexed in Pubmed: 29345112.
27. Pritchett AM, Mahoney DW, Jacobsen SJ, et al. Diastolic dysfunction and left atrial volume: a population-based study. J Am Coll Cardiol. 2005; 45(1): 87–92, doi: 10.1016/j.jacc.2004.09.054, indexed in Pubmed: 15629380.
28. Melenovsky V, Hwang SJ, Redfield MM, et al. Left atrial remodeling and function in advanced heart failure with preserved or reduced ejection fraction. Circ Heart Fail. 2015; 8(2): 295–303, doi: 10.1161/CIRCHEARTFAILURE.114.001667, indexed in Pubmed: 25593126.
29. Almeida P, Rodrigues J, Lourenço P, et al. Left atrial volume index is critical for the diagnosis of heart failure with preserved ejection fraction. J Cardiovasc Med (Hagerstown). 2018; 19(6): 304–309, doi: 10.2459/JCM.0000000000000651, indexed in Pubmed: 29553992.
30. Barandiarán Aizpurua A, Sanders-van Wijk S, Brunner-La Rocca HP, 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): 413–421, doi: 10.1002/ejhf.1614, indexed in Pubmed: 31472035.
31. Kristensen SL, McMurray JJV. Diagnosing heart failure with preserved ejection fraction - what's the score? Eur J Heart Fail. 2020; 22(3): 425–427, doi: 10.1002/ejhf.1764, indexed in Pubmed: 32086989.

32. Li S, Churchill T, Curreri L, et al. Diagnosing HFpEF: validation of a noninvasive diagnostic approach against invasive hemodynamics. Journal of the American College of Cardiology. 2020; 75(11): 911, doi: 10.1016/s0735-1097(20)31538-2.
33. Reddy YNV, Kaye DM, Handoko ML, et al. Diagnosis of Heart Failure With Preserved Ejection Fraction Among Patients With Unexplained Dyspnea. JAMA Cardiol. 2022; 7(9): 891–899, doi: 10.1001/jamacardio.2022.1916, indexed in Pubmed: 35830183.
34. Takagi T. Diastolic stress echocardiography. J Echocardiogr. 2017; 15(3): 99–109, doi: 10.1007/s12574-017-0335-7, indexed in Pubmed: 28271289.
35. Prasad SB, Holland DJ, Atherton JJ. Diastolic stress echocardiography: from basic principles to clinical applications. Heart. 2018; 104(21): 1739–1748, doi: 10.1136/heartjnl-2017-312323, indexed in Pubmed: 30030333.
36. Kim KH, Kane GC, Luong CL, et al. Echocardiographic Diastolic Stress Testing: What Does It Add? Curr Cardiol Rep. 2019; 21(9): 109, doi: 10.1007/s11886-019-1187-8, indexed in Pubmed: 31377869.
37. Nagueh SF, Sun H, Kopelen HA, et al. Hemodynamic determinants of the mitral annulus diastolic velocities by tissue Doppler. J Am Coll Cardiol. 2001; 37(1): 278–285, doi: 10.1016/s0735-1097(00)01056-1, indexed in Pubmed: 11153752.
38. Obokata M, Kane GC, Reddy YNV, et al. Role of Diastolic Stress Testing in the Evaluation for Heart Failure With Preserved Ejection Fraction: A Simultaneous Invasive-Echocardiographic Study. Circulation. 2017; 135(9): 825–838, doi: 10.1161/CIRCULATIONAHA.116.024822, indexed in Pubmed: 28039229.
39. Sud K, Bhatia KS, Vogel B, et al. Prognostic significance of exercise-induced diastolic dysfunction: A systematic review. Echocardiography. 2020; 37(10): 1594–1602, doi: 10.1111/echo.14841, indexed in Pubmed: 32892393.
40. Jong-Won H, Andersen OS, Simseth OA. Diastolic stress test. Invasive and noninvasive testing. JACC: Cardiovascular Imaging 2020;13(1):272-282.
41. Fitzgerald BT, Presneill JJ, Scalia IG, et al. The Prognostic Value of the Diastolic Stress Test in Patients Undergoing Treadmill Stress Echocardiography. J Am Soc Echocardiogr. 2019; 32(10): 1298–1306, doi: 10.1016/j.echo.2019.05.021, indexed in Pubmed: 31377071.
42. Gharacholou SM, Scott CG, Takahashi PY, et al. Left ventricular diastolic function and long-term outcomes in patients with normal exercise echocardiographic findings. Am J Cardiol. 2013; 112(2): 200–207, doi: 10.1016/j.amjcard.2013.03.009, indexed in Pubmed: 23611754.
43. Mandoli GE, Sisti N, Mondillo S, et al. Left atrial strain in left ventricular diastolic dysfunction: have we finally found the missing piece of the puzzle? Heart Fail Rev. 2020; 25(3): 409–417, doi: 10.1007/s10741-019-09889-9, indexed in Pubmed: 31773504.
44. Smiseth OA, Donal E, Boe E, et al. Phenotyping heart failure by echocardiography: imaging of ventricular function and haemodynamics at rest and exercise. Eur Heart J Cardiovasc Imaging. 2023; 24(10): 1329–1342, doi: 10.1093/ehjci/jead196, indexed in Pubmed: 37542477.