

**THE SIGNIFICANCE OF LEFT ATRIAL VOLUME CHANGES AND BRAIN NATRIURETIC
PEPTIDE CONCENTRATIONS DURING DIASTOLIC STRESS ECHOCARDIOGRAPHY IN
THE DIAGNOSIS OF HEART FAILURE WITH PRESERVED EJECTION FRACTION**

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HFpEF patients are defined based on preserved LVEF ($\geq 50\%$), together with the following required criteria: 1. symptoms and signs of HF; 2. elevated natriuretic peptides; 3. additional echocardiographic criteria: objective evidence of structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction and/or elevated LV filling pressures. Calculation and interpretation of the HFA-PEFF score: a total score ≥ 5 points is considered sufficient to establish a diagnosis of HFpEF, whereas a score ≤ 1 point is sufficient to exclude the diagnosis. Scores between 2–4 indicate the need for additional evaluation (step 3 [F1]). Functional testing is of great importance in patients with intermediate score values. Diastolic

stress echocardiography (SET) is considered abnormal if the mean E/e' ratio at peak exercise is ≥ 15 (2 points), with or without TRV > 3.4 m/s. An isolated increase in TRV does not contribute to the scoring system; however, in combination with the above-mentioned rise in E/e', it contributes 3 points to the score. Adding changes in LAVi during diastolic SET increased the sensitivity of the modified score according to the rule-in principle from 32.7% to 33.0%, leading to the conclusion that incorporating LAVi changes into the existing HFA-PEFF score did not significantly improve sensitivity. Adding changes in BNP during diastolic SET increased sensitivity from 32.7% to 56.4%. The specificity of the modified HFA-PEFF score was 95.0%, PPV 96.9%, NPV 44.2%, with an overall test efficiency of 66.7%. Conclusion: Incorporating BNP changes into the existing HFA-PEFF score significantly improves sensitivity. The combined addition of LAVi and BNP changes to the HFA-PEFF score markedly contributes to the improvement of sensitivity for diagnosing HFpEF.

Keywords: HFpEF, HFA-PEFF score, BNP, LAVi

**ZNAČAJ PROMENA ZAPREMINE LEVE PRETKOMORE I KONCENTRACIJA MOŽDANOG
NATRIURETSKOG PEPTIDA TOKOM DIJASTOLNOG STRES-EHOKARDIOGARFSKOG
TESTA U POSTAVLJANJU DIJAGNOZE SRČANE INSUFICIJENCIJE SA OČUVANOM
EJEKCIONOM FRAKCIJOM**

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HFpEF bolesnici su definisani na osnovu očuvane (EFLK $\geq 50\%$), uz kriterijume koje je potrebno ispuniti: 1) simptomi i znaci HF; 2) povišeni natriuretski; 3) dodatni ehokardiografski kriterijumi: objektivan dokaz strukturne i/ili funkcionalne abnormalnosti konzistentan sa prisustvom dijasolne disfunkcije LK/povećanog pritiska punjenja LK. Kalkulacija i interpretacija HFA-PEFF skora: Ukupan rezultat ≥ 5 poena smatra se dovoljnim za postavljanje HFpEF dijagnoze, dok se skor ≤ 1 poena smatra dovoljnim za isključivanje HFpEF dijagnoze. Rezultat 2–4 nas upućuje na dodatne korake (korak 3 (F1)). Funkcionalno testiranje je od velike važnosti kod bolesnika sa intermedijarnim vrednostima predloženog skor sistema. Dijastolni stres-ehokardiografski test

(SET) se smatra abnormalnim ako prosečni odnos E/e' pri maksimalnom opterećenju iznosi ≥ 15 (2 poena), sa ili bez TRV $> 3,4$ m/s. Samo povećanje TRV ne doprinosi skor sistemu, ali u sprezi sa navedenim porastom E/e' doprinosi skor sistemu sa 3 poena. Dodatak promena LAVi tokom dijastolnog SET-a, senzitivnost prema roule-in principu ovako izmenjenog skora se povećala sa 32,7% na 33,0% te možemo zaključiti da dodavanje promene LAVi postojećem skoru HFA PEFF nije značajno doprineo povećanju senzitivnosti. Dodatak promena BNP tokom dijastolnog SET-a, senzitivnost se povećala sa 32,7% na 56,4%. Specifičnost ovakvog HFA PEFF skora je bila 95,0%, PPV 96,9%, NPV 44,2% uz efikasnost testa od 66,7%. Možemo zaključiti da dodavanje promene BNP-a postojećem skoru HFA PEFF značajno doprinosi povećanju senzitivnosti. Dodavanje promene LAVi/BNP-a postojećem skoru HFA PEFF značajno doprinosi povećanju senzitivnosti za postavljanje HFpEF dijagnoze.

Ključne reči: HFpEF, HFA PEFF skor, BNP, LAVi

Introduction

In recent years, consensus has been reached regarding the threshold values of left ventricular ejection fraction (LVEF) used for the classification of heart failure (HF). According to current European and American cardiology society guidelines, HF is categorized as follows: Heart failure with reduced ejection fraction (HFrEF, LVEF $\leq 40\%$); heart failure with preserved ejection fraction (HFpEF, LVEF $\geq 50\%$); and heart failure with mildly reduced ejection fraction (HFmrEF, LVEF 41–49%) (1, 2, 3). According to the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic HF, HFpEF patients are defined by preserved LVEF ($\geq 50\%$) along with additional diagnostic criteria: 1. symptoms and signs of HF, which may not necessarily be present in patients receiving diuretic therapy; 2. elevated natriuretic peptides (NP) (BNP > 35 pg/mL and/or NT-proBNP > 125 pg/mL in patients in sinus rhythm; BNP > 105 pg/mL and/or NT-proBNP > 365 pg/mL in patients with atrial fibrillation [AF]); 3. additional echocardiographic criteria: objective evidence of structural and/or functional abnormalities consistent with LV diastolic dysfunction and/or elevated LV filling pressures (2).

In 2019, the Heart Failure Association (HFA) and ESC published a new diagnostic algorithm for HFpEF—the HFA-PEFF algorithm (4). The threshold values of key non-invasive diastolic dysfunction (DD) parameters are often based on limited scientific data and may sometimes fall into indeterminate ranges. The purpose of the new algorithm is to ensure that the diagnosis or exclusion of HFpEF does not rely on a single parameter and its possible borderline values, but rather on a combination of clinical, laboratory, and imaging markers that together provide significantly greater diagnostic accuracy.

As proposed by HFA/ESC, the algorithm consists of four diagnostic steps (P, E, F1, and F2). **Step 1 (P)** recommends a patient assessment (evaluation of symptoms and signs of HF), measurement of NP and standard laboratory tests, electrocardiography, chest X-ray, and standard echocardiography to assess LVEF and LV dimensions. Since 2022, cardiopulmonary exercise testing (CPET) has also been recommended at this stage to exclude non-cardiac causes of dyspnea (5). **Step 2 (E)** involves detailed echocardiographic evaluation of LV and left atrial (LA) morphology and function, with a focus on LV diastolic function. Echocardiographic criteria in the proposed HFA-PEFF scoring system are divided into two domains—functional and morphological—and further classified as major and minor criteria.

Functional domain: Major criteria: septal $e' < 7$ cm/s or lateral $e' < 10$ cm/s (patients < 75 years); septal $e' < 5$ cm/s or lateral $e' < 7$ cm/s (patients ≥ 75 years); average $E/e' \geq 15$; or tricuspid regurgitation velocity (TRV) > 2.8 m/s (pulmonary artery systolic pressure, PASP > 35 mmHg). Minor criteria: average E/e' 9–14 or GLS $< 16\%$. **Morphological domain:** Major criteria: LAVi > 34 mL/m² (sinus rhythm) or LAVi > 40 mL/m² (AF); or LV mass index (LVMI) ≥ 149 g/m² for men or ≥ 122 g/m² for women, with relative wall thickness (RWT) > 0.42 . Minor criteria: LAVi 29–34 mL/m² (sinus rhythm) or LAVi 34–40 mL/m² (AF); or LVMI ≥ 115 g/m² for men or ≥ 95 g/m² for women; or RWT > 0.42 ; or LV wall thickness ≥ 12 mm. **Biomarker domain:** Major criteria: NT-proBNP > 220 pg/mL or BNP > 80 pg/mL (sinus rhythm); NT-proBNP > 660 pg/mL or BNP > 240 pg/mL (AF). Minor criteria: NT-proBNP 125–220 pg/mL or BNP 35–80 pg/mL (sinus rhythm); NT-proBNP 365–660 pg/mL or BNP 105–240 pg/mL (AF). It should be noted that precise threshold values for NP are not universally defined, as different studies have used varying cut-off values. What remains consistent is that NP levels are approximately 3–3.5 times higher in AF compared to sinus rhythm.

Calculation and interpretation of the HFA-PEFF score: The proposed scoring system comprises the functional, morphological, and biomarker domains. Within each domain, a major criterion scores 2 points, while a minor criterion scores 1 point. Each domain can contribute a maximum of 2 points (if a major criterion is present) or 1 point (if only minor criteria are present). If multiple major criteria are present within one domain, the domain still contributes only 2 points; similarly, multiple minor criteria contribute a maximum of 1 point. Major and minor criteria within the same domain are not additive. Points are only summed when derived from different domains. A total score ≥ 5 points is sufficient to establish a diagnosis of HFpEF, while a score ≤ 1 point is sufficient to exclude HFpEF. A score of 2–4 indicates the need for further evaluation (step 3 [F1]).

Functional testing – diastolic stress echocardiography: Functional testing plays a crucial role in patients with intermediate HFA-PEFF scores. A diastolic stress echocardiographic test (SET) is considered abnormal if the average E/e' ratio at peak exercise is ≥ 15 (2 points), with or without TRV > 3.4 m/s. An isolated increase in TRV does not contribute to the score, but when combined with an increase in E/e' , it contributes 3 points (4).

Objective

To determine the HFA-PEFF algorithm score and assess its sensitivity and specificity for diagnosing heart failure with preserved ejection fraction (HFpEF). Furthermore, to evaluate whether the addition of novel echocardiographic parameters and laboratory variables to the HFA-PEFF score improves its sensitivity and specificity for diagnosing HFpEF.

Methodology

The study was conducted at the Institute for Treatment and Rehabilitation "Niška Banja," Clinic for Cardiovascular Diseases, between December 2019 and December 2021. It was designed as a randomized, open-label, controlled, prospective study. A total of 150 participants of both sexes, aged over 18 years, were enrolled. Of these, 110 constituted the clinical HFpEF group, diagnosed according to ESC/HFA guidelines for the diagnosis and treatment of acute and chronic heart failure (2016) (6), and 40 participants formed the control group (healthy individuals matched by age and sex).

Prior to enrollment, all participants were informed about the study purpose and signed written informed consent before undergoing any procedures. The study was approved by the Ethics Committee of the Faculty of Medicine, University of Niš, and the Ethics Board of the Institute for Treatment and Rehabilitation "Niška Banja." It was conducted in accordance with the Declaration of Helsinki and good clinical practice principles.

All HFpEF patients had been previously hospitalized and treated at the Institute for Treatment and Rehabilitation "Niška Banja," with symptoms and signs of acute HF. The diagnosis of acute decompensated HF was made at admission based on ESC/HFA recommendations (2016), and was required to be confirmed at hospital discharge. Patients received optimal guideline-directed medical therapy during and after hospitalization (6).

Participants were enrolled 6–8 weeks after the index event, in a compensated HF state. Following consent and clinical examination, blood samples were obtained for laboratory testing, stroke volume (SV) and blood pressure (BP) were measured, and a 12-lead ECG was performed. All participants then underwent diastolic stress echocardiography (SET) in the semi-supine position on a bicycle ergometer. Echocardiography was performed: at baseline; during stress when HR >100–110 bpm or when limiting symptoms (fatigue, dyspnea, chest pain) occurred; during recovery, 15 minutes post-exercise, according to study protocol. Blood samples for BNP measurement were collected after the exercise phase.

HFpEF diagnosis. HFpEF was diagnosed according to ESC/HFA guidelines (2016) (6), requiring the following: presence of HF symptoms and/or signs (not always present in early disease or in patients on diuretics); LVEF $\geq 50\%$ (echocardiographic); elevated NP (BNP >35 pg/mL and/or NT-proBNP >125 pg/mL); at least one additional criterion: relevant structural heart disease (LAVi >34 mL/m² or LVMI ≥ 115 g/m² in men and ≥ 95 g/m² in women) or proven LV diastolic dysfunction ($E/e' \geq 13$ or average $e' < 9$ cm/s). If results were inconclusive, diastolic SET was recommended in patients with unexplained dyspnea and grade I DD at rest. A test was considered positive if ≥ 3 criteria were met: $E/e' > 14$ or septal $E/e' > 15$, TRV > 2.8 m/s, and septal $e' < 7$ cm/s (6, 7).

Echocardiographic assessment. All participants underwent comprehensive two-dimensional echocardiography (2DE) using conventional methods. Imaging was performed on an Esaote-MyLab Alpha eHD Crystalline series 7400 system with a phased-array transducer (1–4 MHz). 2D cine loops were recorded for off-line analysis, with at least three cardiac cycles at end-expiration, R-wave as reference, and frame rate 40–80 fps. Continuous ECG monitoring was performed, and HR values were automatically incorporated into echocardiographic parameters. Body surface area was used for indexation of parameters. All 2DE measurements were performed according to ASE/EACVI guidelines for transthoracic echocardiography and chamber quantification (8, 9).

Diastolic stress echocardiography. According to study protocol, all participants underwent diastolic SET in the semi-supine position on a Schiller ergometer (Switzerland). Testing was performed under full medical therapy, but without beta-blockers (discontinued 24 h before testing). Participants abstained from coffee and smoking prior to testing. Stress echocardiography followed the Cardiff-MEDIA protocol (with minor modifications to allow sufficient time for imaging) (10, 11, 12). The ramp protocol began at 15 W, with increments of 5 W every minute and cadence maintained at 55–65 rpm. Once HR exceeded 100–110 bpm, workload was maintained (3–5 min) to enable echocardiographic imaging and BNP sampling. Recovery lasted 10–15 minutes. Echocardiography was performed at baseline, during stress, and during recovery as described. Continuous ECG monitoring and BP measurements (every 2 minutes) were performed throughout. The test was terminated early if typical angina, segmental wall motion abnormalities, severe dyspnea, dizziness, hypotension (SBP drop >10 mmHg), hypertension (SBP >220 mmHg), significant ventricular arrhythmias, or ischemic ST-segment changes (ST elevation or ≥ 1.0 mm horizontal/downsloping ST depression at 80 ms after J point in ≥ 3 cycles) occurred (10, 11, 12).

Analysis and calculation of the HFA-PEFF score. Scoring was performed according to ESC/HFA recommendations (4). HFA-PEFF score at rest (Score 1) and post-SET (Score 2) were calculated. For this study, three modified scores were developed: Score 3: addition of maximal LAVi during SET;

Score 4: addition of maximal BNP during SET; Score 5: addition of combined maximal LAVi/BNP during SET. Contribution of added parameters was reassessed using expert-defined cut-off values. Minimal changes in LAVi and BNP required for reclassification were defined statistically (median changes in the HFpEF group during SET).

Statistical analysis. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall test performance were calculated. Data were tabulated and graphically presented as mean $\pm$ SD, median with interquartile range, or absolute/relative frequencies. Normality was tested using the Kolmogorov-Smirnov test. Between-group comparisons used Student's t-test (parametric) or Mann-Whitney U test (non-parametric). Paired comparisons (before/after SET) used paired t-test. Correlations were assessed using Pearson's or Spearman's coefficients depending on data distribution. A p-value <0.05 was considered statistically significant. Analyses were performed with SPSS 16.0 (SPSS Inc., Chicago, IL, USA).

Results

A total of 110 patients with HFpEF (clinical HFpEF group) and 40 healthy individuals (control group) were included in the study. The mean age of all study participants was 63.92 ± 8.88 years (range: 42–80 years). Patients with HFpEF were significantly older compared to the control group ($p = 0.020$). In the clinical group, males were more prevalent (51.8%), whereas in the control group females predominated (55%); however, the groups were balanced with respect to sex distribution ($p = 0.580$) (Table 1).

Table 1. Demographic and Anthropometric Parameters by Study Group

Parameter	Clinical group n=110	Control group n=40	p [#]
Years*	65,08 $\pm$ 7,99	60,73 $\pm$ 10,41	0,020
Gender			
Male, n (%)	57 (51,8)	18 (45,0)	0,580
Female, n (%)	53 (48,2)	22 (55,0)	
BMI (kg/m ²)*	29,95 $\pm$ 3,75	24,28 $\pm$ 2,98	<0,001

[#]t-test; *arithmetic mean $\pm$ standard deviation; BMI, Body Mass Index

Analysis of echocardiographic parameters showed that values of IVS, PW, RWT, and LVMI were significantly higher in patients with HFpEF compared to controls. LVEF values were significantly lower in the HFpEF group ($p<0.001$). GLS values were also significantly reduced in HFpEF patients compared to controls ($p<0.001$) (Table 2).

Table 2. Basic Echocardiographic and Laboratory Parameters According to Study Groups

Parameter	Clinical group n=110	Control group n=40	p [#]
LVEF (%) [*]	57,24±6,11	61,5±4,56	<0,001
GLS (%) [*]	-17,06±0,98	-20,49±1,11	<0,001
IVS (mm) [*]	13,49±1,39	11,55±1,64	<0,001
PW (mm) [*]	11,39±1,14	9,91±1,38	<0,001
IVS/PW (mm) ≥11 M, ≥10 F n (%)	109(99,1)	26(66,7)	<0,001 [‡]
RWT [*]	0,45±0,05	0,40±0,05	<0,001
RWT >0,42 n (%)	68 (61,8)	14 (42,5)	=0,006 [‡]
LVMI (g/m ²) [*]	129,64±24,09	104,31±24,39	<0,001
LVMI (g/m ²) >102 M, >88 F n (%)	105 (95,5)	25(62,5)	<0,001 [‡]
PASP (mmHg) [*]	23,43±6,66	21,21±6,4	0,071
TRV (m/s) [*]	1,72±0,51	1,59±0,56	0,186
BNP rest (pg/mL) [*]	40,56±33,07	12,59±7,5	0,001
BNP peak (pg/mL) [*]	74,12±45,28	19,37±8,74	<0,001

#t-test; ^{*}arithmetic mean±standard deviation; [‡]Chi-square test; ^{*}Fisher's test; M, Male; F, Female; LVEF, Left Ventricular Ejection Fraction; GLS, Global Longitudinal Strain; IVS, Interventricular Septum; PW, Posterior Wall; RWT, Relative Wall Thickness; LVMI, Left Ventricular Mass Index; PASP, Pulmonary Artery Systolic Pressure; TRV, Tricuspid regurgitation velocity; BNP, Brain Natriuretic Peptide; rest, value of the examined parameter at the beginning of the diastolic SET; peak, value of the examined parameter at maximal load during the diastolic SET

The mean BNP increase in the HFpEF group was 33.55 ± 23.52 pg/mL (median 28.7 pg/mL), whereas in the control group it was 6.77 ± 2.64 pg/mL ($p<0.001$). Eleven patients (10%) in the HFpEF group had BNP >80 pg/mL, and 36 (32.72%) had BNP values >35 and <80 pg/mL. All control subjects had BNP levels <35 pg/mL ($p<0.001$) (Table 2).

LAVi rest and LAVi peak values were significantly higher in HFpEF patients compared to controls. LAVi values increased significantly during stress testing both in HFpEF patients ($p<0.001$) and in controls ($p<0.001$) (Table 3). The mean increase in LAVi in the clinical group was 4.26 ± 2.01 mL/m² versus 2.01 ± 1.85 mL/m² in controls ($p<0.001$). The median LAVi change in the HFpEF group was 4 mL/m².

Values of e' med rest, e' med peak, e' lat rest, e' lat peak, e' avg rest, and e' avg peak were significantly lower in HFpEF patients than in controls (all $p<0.001$). Conversely, E/e' med peak,

E/e' lat peak, and E/e' avg peak values were significantly higher in the HFpEF group (all $p < 0.001$) (Table 3).

During testing, e' med, e' lat, e' avg, E/e' med, E/e' lat, and E/e' avg increased significantly in HFpEF patients (all $p < 0.001$). In the control group, e' med, e' lat, e' avg, and E/e' lat also changed significantly (all $p < 0.001$, except E/e' avg, $p = 0.002$) (Table 3).

Table 3. Left Ventricular Diastolic Function Echocardiographic Parameters and Their Changes During Diastolic Stress Echocardiography (DSE) in the Study Groups

Parameter*	Clinical group n=110	Control group n=40	p [#]
e' med (m/s) rest	0,07±0,02	0,09±0,02	<0,001
e' med (m/s) peak	0,08±0,02	0,11±0,02	<0,001
p ^{**}	<0,001	<0,001	
e' lat (m/s) rest	0,09±0,02	0,11±0,02	<0,001
e' lat (m/s) peak	0,10±0,02	0,13±0,02	<0,001
p ^{**}	<0,001	<0,001	
e' avg (m/s) rest	0,08±0,02	0,10±0,02	<0,001
e' avg (m/s) peak	0,09±0,02	0,12±0,02	<0,001
p ^{**}	<0,001	<0,001	
E/e' avg rest	7,58±2,27	7,83±1,5	0,444
E/e' avg peak	11,47±3,38	8,17±1,48	<0,001
p ^{**}	<0,001	0,131	
LAVi (mL/m ²) rest	28,78±6,85	26,13±5,37	0,028
LAVi (mL/m ²) peak	33,05±7,16	28,14±5,12	<0,001
p ^{**}	<0,001	<0,001	
TRV (m/s) rest	1,72±0,51	1,59±0,56	0,186
TRV (m/s) peak	2,55±0,62	1,96±0,55	<0,001
p ^{**}	<0,001	<0,001	
PASP (mmHg) rest	23,43±6,66	21,21±6,40	0,071
PASP (mmHg) peak	36,11±10,83	23,42±6,40	<0,001
p ^{**}	<0,001	<0,001	

rest, value of the examined parameter at the beginning of the diastolic SET; peak, value of the examined parameter at maximal load during the diastolic SET; avg, average; p[#] between-group t-test/Mann-Whitney test; p^{**} between rest and peak repeated-measures t-test / Wilcoxon test; *arithmetic mean±standard deviation; PASP, Pulmonary Artery Systolic Pressure; TRV, Tricuspid regurgitation velocity; LAVi, Left Atrial Volume Index

In the clinical group, 58 patients (52.7%) had e' med rest <0.07 m/s, compared with 5 (12.5%) in the control group ($p < 0.001$). Similarly, 73 HFpEF patients (66.4%) had e' lat rest <0.10 m/s, versus 4 (10%) in controls ($p < 0.001$).

No participants in either group had E/e' ≥15 at rest; however, 28 patients (25.45%) in the HFpEF group had E/e' values 9–14, versus 7 (17.5%) in controls ($p = 0.424$). During stress, E/e' ≥15

increased in 17 HFpEF patients (15.45%), whereas none of the controls reached this threshold ($p < 0.001$).

TRV peak values were significantly higher in HFpEF patients compared to controls ($p < 0.001$), although resting values did not differ between groups. The mean TRV increase in the HFpEF group was 0.83 ± 0.46 m/s, compared with 0.36 ± 0.20 m/s in controls ($p < 0.001$).

Analysis of the HFA-PEFF score in clinical and control groups

The distribution of baseline HFA-PEFF score categories differed significantly between groups. In the clinical group, more than half of patients (65.5%) had an intermediate score and 26% a high score, whereas in the control group the majority (75.0%) had a low score (Table 4).

Table 4. Initial HFA-PEFF Score in Relation to Study Groups (Score 1)

Parameter	Clinical group n=110	Control group n=40	p [#]
Low (0-1), n (%)	12 (10,9)	30 (75,0)	<0,001
Intermediate (2-4) , n (%)	72 (65,5)	10 (25,0)	
High (5+), n (%)	26 (23,6)	0 (0,0)	

[#]Chi-square test

After diastolic SET, the distribution of HFA-PEFF score categories also differed significantly. In the clinical group, 56.4% had an intermediate score and 32.7% a high score, while in controls the majority (75.0%) remained in the low-score category (Table 5). In the HFpEF group, 17 patients (15.45%) developed $E/e' \geq 15$; TRV > 3.4 m/s was observed in 9 patients (8.18%), but only 2 patients (1.82%) had both TRV elevation and $E/e' \geq 15$. BNP rose to > 80 pg/mL in 34 patients (30.9%) and to > 35 – < 80 pg/mL in 33 patients (30.0%). Nineteen patients (17.27%) moved into a higher LAVi category (> 34 mL/m²), and 2 patients (1.81%) into the 29–34 mL/m² category.

Table 5. HFA-PEFF Score After Diastolic Stress Echocardiography in Relation to Study Groups (Score 2)

Parameter	Clinical group n=110	Control group n=40	p [#]
Low (0-1), n (%)	12 (10,9)	30 (75,0)	<0,001
Intermediate (2-4) , n (%)	62 (56,4)	10 (25,0)	
High (5+), n (%)	36 (32,7)	0 (0,0)	

[#]Chi-square test

When LAVi after diastolic SET was added as a new variable, score distribution again differed significantly. In the clinical group, 56.4% had an intermediate score and 33.6% a high score, while most controls (75.0%) remained in the low-score category (Table 6).

Table 6. HFA-PEFF Score After Diastolic Stress Echocardiography with LAVi (Score 3) in Relation to Study Groups

Parameter	Clinical group n=110	Control group n=40	p [#]
Low (0-1), n (%)	11 (10.0)	30 (75.0)	<0,001
Intermediate (2-4) , n (%)	62 (56.4)	10 (25.0)	
High (5+), n (%)	37 (33.6)	0 (0.0)	

#Chi-square test;

Table 7. HFA-PEFF Score After Diastolic Stress Echocardiography with BNP (Score 4) in Relation to Study Groups

Parameter	Clinical group n=110	Control group n=40	p [#]
Low (0-1), n (%)	6 (5.5)	29 (72.5)	<0,001
Intermediate (2-4) , n (%)	42 (38.2)	9 (22.5)	
High (5+), n (%)	62 (56.4)	2 (5.0)	

#Chi-square test

When BNP after diastolic SET was added as a new variable, score distribution showed that more than half of the HFpEF patients (56.4%) had a high score, while 72.5% of controls remained in the low-score category (Table 7).

When both BNP and LAVi after diastolic SET were included, the distribution again differed significantly: 60.9% of HFpEF patients had a high score, while 72.5% of controls remained in the low category (Table 8).

Table 8. HFA-PEFF Score After Diastolic Stress Echocardiography with LAVi/BNP (Score 5) in Relation to Study Groups

Parameter	Clinical group n=110	Control group n=40	p [#]
Low (0-1), n (%)	5 (4.5)	29 (72.5)	<0,001
Intermediate (2-4) , n (%)	38 (34.5)	9 (22.5)	
High (5+), n (%)	67 (60.9)	2 (5.0)	

#Chi-square test

A low HFA-PEFF score (0–1; rule-out approach) excluded HFpEF with a sensitivity of 89.1% and a positive predictive value of 90.7% (Table 9, Figure 1). Test efficiency was 85.3%.

Table 9. Performance of HFA-PEFF Scores for HFpEF Diagnosis – “Roule-Out” Approach

	Score 1	Score 2	Score 3	Score 4	Score 5
Sensitivity (%)	89,1	89,1	90,0	94,5	95,5
Specificity (%)	75,0	75,0	75,0	72,5	72,5
PPV (%)	90,7	90,7	90,8	90,4	90,5
NPV (%)	71,4	71,4	73,2	82,9	85,3
Accuracy	85,3	85,3	86,0	88,7	89,3

PPV, Positive Predictive Value; NPV, Negative Predictive Value; Intermediate and high-risk scores considered as positive values in the study population

A high HFA-PEFF score (>5; rule-in approach) identified HFpEF patients with 100% specificity and 100% positive predictive value (Table 10, Figure 1). Test efficiency was 44%.

Table 10. Performance of HFA-PEFF Scores for HFpEF Diagnosis – “Roule-In” Approach

	Score 1	Score 2	Score 3	Score 4	Score 5
Sensitivity (%)	23.6	32.7	33.0	56.4	60.9
Specificity (%)	100.0	100.0	100.0	95.0	95.0
PPV (%)	100.0	100.0	100.0	96.9	97.1
NPV (%)	32.3	35.1	34.8	44.2	46.9
Accuracy	44.0	50.7	50.7	66.7	70.0

PPV, Positive Predictive Value; NPV, Negative Predictive Value; High-risk score considered as a positive value in the study population

Changes in HFA-PEFF score categories in the HFpEF group are presented in Figure 1.

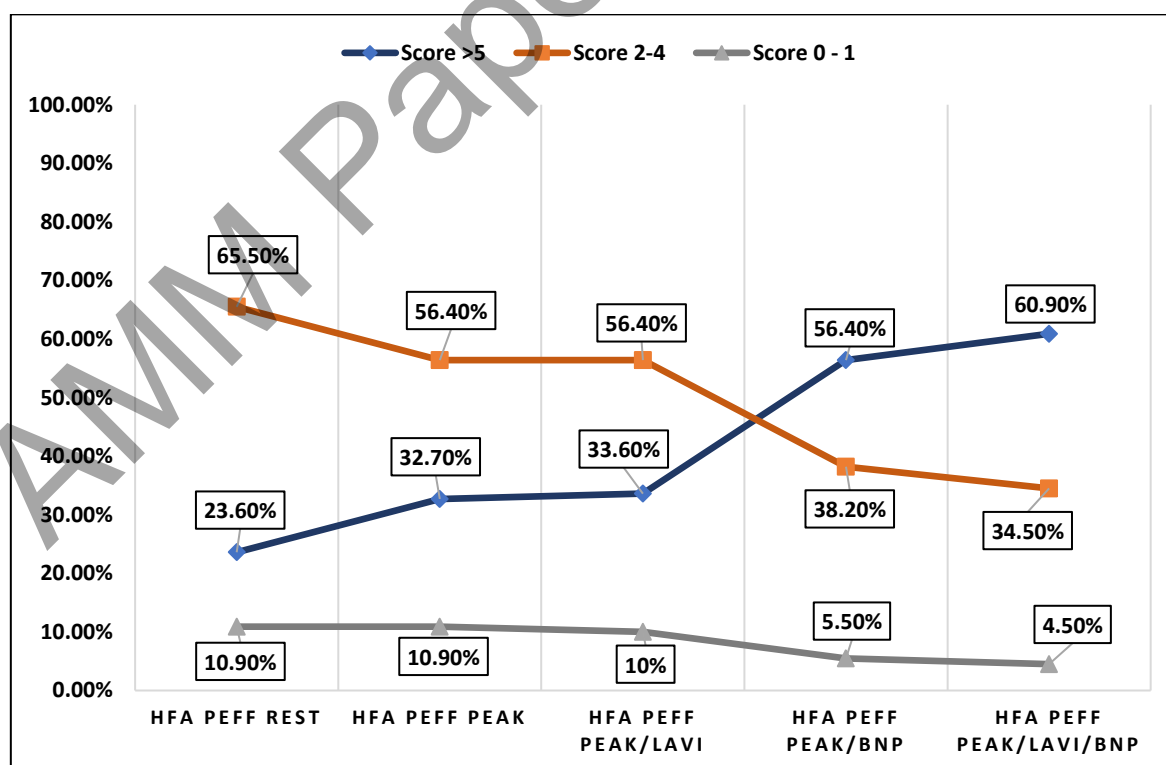


Figure 1. Change in HFA-PEFF Score in the HFpEF Patient Group. HFA-PEFF: Heart Failure Association–PEFF score for the diagnosis of HFpEF; rest, value of the assessed parameter at the

start of the diastolic stress echocardiography (SET); peak, value of the assessed parameter at maximal exercise during SET; LAVi; Left Atrial Volume Indexed; BNP; Brain Natriuretic Peptide

Discussion

The Heart Failure Association and the European Society of Cardiology published a new algorithm for the diagnosis of HFpEF (the HFA-PEFF algorithm) in 2019 (4). Following its publication, the HFA-PEFF score underwent validation both in randomized controlled cohorts and observational population studies, assessing the sensitivity and specificity of the proposed score for establishing the HFpEF diagnosis, as well as its prognostic value for adverse cardiovascular events (13).

The HFA-PEFF score was validated in two prospective cohorts (Maastricht and Chicago) with confirmed HFpEF diagnoses. The mean age in the Maastricht cohort was 76.3 years, while in the Chicago cohort it was 66.13 years. Both cohorts had a high prevalence of AF (58% and 35%, respectively) and hypertension (86% and 76%). Notably, patients with NYHA class II and III (40–60%) were highly represented, and elevated NP levels were observed (NT-proBNP 799 pg/mL in Maastricht and BNP 222 pg/mL in Chicago). These data indicate that the study population was older, with decompensated or subcompensated HF (NYHA class III and high NP levels), which likely contributed to the higher sensitivity of the HFA-PEFF score in diagnosing HFpEF (13).

Despite the inclusion of patients with more severe HF, 36% of participants remained in the intermediate zone (HFA-PEFF score 2–4), requiring additional diagnostic testing. Sensitivity for ruling out HFpEF was 99% with an NPV of 73%, while rule-in sensitivity for confirming the diagnosis was 69%, with a PPV of 98%.

The HFA-PEFF score was further evaluated in the large German observational population-based study DIAST-CHF, which included 1,937 patients with suspected HFpEF. This analysis showed that 58.8% of patients fell into the intermediate group, while 29.58% were in the high-score group. This resulted in a considerable decrease in sensitivity for diagnosing HFpEF, but it realistically reflected the diagnostic utility of the HFA-PEFF score in daily clinical practice. The majority of patients in this cohort required further diagnostic evaluation to establish the HFpEF diagnosis (14). Our analysis demonstrated that most patients in the HFpEF group (65.5%) had intermediate scores (2–4), 23.6% had high scores (≥ 5), and 10.9% had low scores (≤ 1).

Analysis of functional, morphological, and biomarker criteria showed that the functional domain contributed most to higher scores, with reduced values of e' med. and e' lat. found in 52.7% and 66.4% of HFpEF patients, respectively. Within the functional domain, $E/e' \geq 15$ at rest was not observed, while $TRV > 2.8$ m/s or $PASP > 35$ mmHg was found in 9 patients (8.18%), of which

only 7 (6.36%) contributed 2 points to the functional domain. In the morphological domain, LAVi contributed most, with 20.9% of patients showing values $>34 \text{ mL/m}^2$. $\text{LVMI} \geq 149 \text{ g/m}^2$ for men and $\geq 122 \text{ g/m}^2$ for women with $\text{RWT} > 0.42$ had little impact. In the biomarker domain, mean BNP levels in the HFpEF group were 40.56 pg/mL ; $\text{BNP} > 80 \text{ pg/mL}$ was found in 10% of patients, and 32.72% had BNP levels between 35–80 pg/mL .

According to the rule-out principle, this scoring system had high sensitivity (89.1%) for excluding HFpEF and an excellent PPV of 90.7%, while NPV was 71.4%; overall test efficiency was also very high at 85.3%. According to the rule-in principle, sensitivity for diagnosing HFpEF was 23.6%, with a PPV of 100% and an NPV of 32.3%; overall test efficiency was 44.0%.

These results are consistent with the DIAST-CHF study (14) but differ significantly from the validation analysis of the Maastricht and Chicago cohorts (13). Our HFpEF patients were on average 10 years younger, with prior AF episodes present in only 14.5% and no active AF at inclusion (since AF at baseline was an exclusion criterion). In contrast, AF prevalence was 58% in the Maastricht cohort. Most of our patients were NYHA class I (74.5%) with no class III or IV cases, whereas 40–59% of patients in the validation cohorts were class II or III. NP levels in the validation cohorts were also markedly higher than in our study. Taken together, our HFpEF patients were younger, with better-controlled HF and significantly lower NYHA class, reflecting better functional status. These differences likely explain the lower sensitivity of the initial HFA-PEFF score in our HFpEF group.

After diastolic SET, 36 patients (32.7%) in the HFpEF group had high scores, while 62 (56.4%) remained in the intermediate range. Echocardiographic analysis showed that 17 patients (15.45%) developed $\text{E/e}' \geq 15$; TRV increased $> 3.4 \text{ m/s}$ in 9 patients (8.18%), but this coincided with $\text{E/e}' \geq 15$ in only 2 patients (1.82%). Sensitivity of the score for diagnosing HFpEF increased from 23.6% to 32.7%, with a specificity of 100%, PPV 100%, NPV 35.1%, and test efficiency of 50.7%.

According to the current HFA-PEFF scoring system and diagnostic algorithm (94), only two echocardiographic variables ($\text{E/e}'$ and TRV) are evaluated after diastolic SET. However, previous studies have highlighted the significance of different LA responses to exercise (three phenotypes) (15), as well as the value of BNP changes during exercise testing (16, 17).

One of the aims of our analysis was to incorporate additional variables after diastolic SET, specifically evaluating changes in LAVi and BNP, and assessing their potential for patient reclassification and improving the sensitivity and specificity of the HFA-PEFF score. The first

requirement was to determine cut-off values for minimal changes: the median change in LAVi (4 mL/m²) and BNP (28.7 pg/mL) in the HFpEF group. Patients were then reclassified into higher morphological or biomarker categories accordingly. BNP rose to >80 pg/mL in 34 patients (30.9%) and into the 35–80 pg/mL range in 33 patients (30.0%). Nineteen patients (17.27%) shifted into the higher LAVi category (>34 mL/m²), while 2 patients (1.81%) shifted into the intermediate category (>29 and <34 mL/m²).

When LAVi changes during diastolic SET were added to the score, only one patient reclassified into the high-score group (33.6%), with the proportion of intermediate scores unchanged (56.4%). Sensitivity by the rule-in principle increased marginally from 32.7% to 33.0%, suggesting that LAVi changes did not significantly improve sensitivity.

When BNP changes were added, the distribution shifted markedly: the high-score group increased from 36 (32.7%) to 62 patients (56.4%). This significantly improved rule-in sensitivity, which increased from 32.7% to 56.4%. Specificity remained 95.0%, PPV 96.9%, NPV 44.2%, with test efficiency of 66.7%. Thus, BNP changes significantly enhanced sensitivity of the HFA-PEFF score. Finally, when both LAVi and BNP changes during diastolic SET were added, the high-score group increased from 36 (32.7%) to 67 patients (60.9%). This further improved rule-in sensitivity from 32.7% to 60.9%. Specificity was 95.0%, PPV 97.1%, NPV 46.9%, with an overall efficiency of 70.0%. These findings suggest that including both LAVi and BNP changes in the HFA-PEFF score significantly increases sensitivity for diagnosing HFpEF.

Conclusion

Analysis of the HFA-PEFF score and evaluation of its sensitivity and specificity for diagnosing HFpEF demonstrated a progressive increase in sensitivity, which nearly doubled in the HFpEF group. Further analysis of echocardiographic variables and assessment of their changes during diastolic SET, along with patient reclassification, is warranted to improve the diagnostic sensitivity of the HFA-PEFF score for HFpEF.

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