

Assessing Strategies for Heart Failure with Preserved Ejection Fraction at the Outpatient Clinic

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Abstract

Background: Heart failure with preserved ejection fraction (HFPEF) is the most common form of heart failure (HF), its diagnosis being a challenge to the outpatient clinic practice.

Objective: To describe and compare two strategies derived from algorithms of the European Society of Cardiology Diastology Guidelines for the diagnosis of HFPEF.

Methods: Cross-sectional study with 166 consecutive ambulatory patients (67.9 ± 11.7 years; 72% of women). The strategies to confirm HFPEF were established according to the European Society of Cardiology Diastology Guidelines criteria. In strategy 1 (S1), tissue Doppler echocardiography (TDE) and electrocardiography (ECG) were used; in strategy 2 (S2), B-type natriuretic peptide (BNP) measurement was included.

Results: In S1, patients were divided into groups based on the E/E' ratio as follows: GI, E/E' > 15 (n = 16; 9%); GII, E/E' 8 to 15 (n = 79; 48%); and GIII, E/E' < 8 (n = 71; 43%). HFPEF was confirmed in GI and excluded in GIII. In GII, TDE [left atrial volume index (LAVI) ≥ 40 mL/m²; left ventricular mass index (LVMI) > 122 for women and > 149 g/m² for men] and ECG (atrial fibrillation) parameters were assessed, confirming HFPEF in 33 more patients, adding up to 49 (29%). In S2, patients were divided into three groups based on BNP levels. GI (BNP > 200 pg/mL) consisted of 12 patients, HFPEF being confirmed in all of them. GII (BNP ranging from 100 to 200 pg/mL) consisted of 20 patients with LAVI > 29 mL/m², or LVMI ≥ 96 g/m² for women or ≥ 116 g/m² for men, or E/E' ≥ 8 or atrial fibrillation on ECG, and the diagnosis of HFPEF was confirmed in 15. GIII (BNP < 100 pg/mL) consisted of 134 patients, 26 of whom had the diagnosis of HFPEF confirmed when GII parameters were used. Measuring BNP levels in S2 identified 4 more patients (8%) with HFPEF as compared with those identified in S1.

Conclusion: The association of BNP measurement and TDE data is better than the isolated use of those parameters. BNP can be useful in identifying patients whose diagnosis of HF had been previously excluded based only on TDE findings. (Arq Bras Cardiol. 2014; 103(3):231-237)

Keywords: Heart Failure; Ambulatory Care; Echocardiography, Doppler; Natriuretic Peptides.

Introduction

Heart failure with preserved ejection fraction (HFPEF) is currently the most common form of heart failure (HF), mainly because of the accelerated population aging and high prevalence of comorbidities. Morbidity and mortality of HFPEF are elevated, similarly to those of HF with reduced ejection fraction¹. Diagnosing HFPEF is one of the great challenges in outpatient clinic practice, in which the patient usually has intolerance to effort and evidence of neither pulmonary

nor systemic congestion¹⁻³. Despite the lack of an effective treatment^{4,5}, it has been well established in the literature that patients with HFPEF should benefit from the control of risk factors present in HFPEF⁶⁻⁸.

The European Society of Cardiology Diastology Guidelines has proposed updated algorithms for the diagnosis and exclusion of HFPEF in ambulatory patients by using tissue Doppler echocardiography (TDE) and measuring plasma levels of natriuretic peptides⁹. That systematization in Brazil is still little used by outpatient clinicians, mainly because of the difficulty in having access to TDE and natriuretic peptide measurements.

This study was aimed at describing and comparing two strategies, one of which with no measurement of B-type natriuretic peptide (BNP), both derived from the algorithms proposed by the European Society of Cardiology Diastology Guidelines⁹ for the diagnosis of HFPEF in ambulatory patients with signs or symptoms of HF.

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Methods

Population

This is a cross-sectional study with non-probability sampling. A convenience sample was selected and included 166 consecutive ambulatory patients with clinical suspicion of HF, assessed from June 2008 to October 2010. The patients had left ventricular ejection fraction (LVEF) \geq 50%.

In this study, we established two strategies [strategy 1 and strategy 2 (S1 and S2, respectively)] based on the algorithms of the European Society of Cardiology Diastology Guidelines to confirm the diagnosis of HFPEF, which requires the following conditions to be satisfied: signs or symptoms of HF; LVEF \geq 50%; left ventricular end-diastolic volume index (LVEDVI) \leq 97 mL/m²; and diastolic dysfunction. In S1, TDE and electrocardiography (ECG) parameters were used; in S2, in addition to those TDE and ECG parameters, BNP measurements were used⁹.

In S1, diastolic dysfunction was diagnosed by use of TDE and based on an E/E' ratio $>$ 15. If the E/E' ratio was between 8 and 15, suggesting diastolic dysfunction, other TDE measurements, such as LV mass index (LVMI, $>$ 122 g/m² and $>$ 149 g/m² for women and men, respectively), left atrial volume (LAV) index (LAVI, $>$ 40 mL/m²) and E/A ratio $<$ 0.5, with deceleration time of the E wave (DT) $>$ 280 ms, were used to confirm the diagnosis. Atrial fibrillation on ECG with an E/E' ratio between 8 and 15 also confirmed the diagnosis of HFPEF⁷.

In S2, BNP measurements were initially combined with the TDE and ECG parameters already described.

Patients with severe heart valve disease, definitive pacemaker, pericardial diseases, severe chronic obstructive pulmonary disease submitted to heart surgery in the last six months were excluded from this study.

Tissue Doppler Echocardiography

Tissue Doppler echocardiography was performed with a Vivid 7 device (GE Medical Systems, Horten, Norway), and analyzed with the EchoPAC software by an experienced observer with no previous knowledge of the other results. The procedure was performed according to the recommendations for chamber quantification of the American Society of Echocardiography (ASE) and the European Association of Echocardiography (EAE)¹⁰. Systolic function was assessed by measuring LVEF.

The LAV indexed to body surface was obtained by use of the biplanar method of discs (modified Simpson's rule) with four- and two-chamber apical view during the end of left ventricular systole. The parameters of diastolic function were estimated by using the mean of five consecutive heartbeats. The initial (E) and late (A) transmitral flow and the DT of the E wave were measured. The myocardial relaxation velocity at the beginning of diastole (E') was measured by use of TDE on the septal and lateral segments of the mitral ring, and the mean of those measurements was obtained. All exams were digitally recorded for future analyses and reviews.

Electrocardiography

All patients underwent 12-lead ECG (Dixtal, Brazil) at rest to identify the presence of atrial fibrillation.

B-type natriuretic peptide

BNP was measured in whole blood samples by using Alere Triage BNP Test (Biosite, USA), which is a rapid fluorescence immunoassay to be used with the Triage Meter for the quantitative measurement of BNP. The BNP values were expressed as pg/mL.

Statistical analysis

The statistical analysis was performed using the Statistical Package for the Social Science® (SPSS®) software, version 17.0. Continuous variables with normal distribution were expressed as means \pm standard deviation, and the differences were assessed with Student *t* test or Analysis of Variance (ANOVA). Continuous variables whose distributions were not normal were presented as medians, and the differences were assessed with Mann-Whitney U test or Kruskal-Wallis-H test. Categorical variables were presented as absolute and relative frequencies, and the differences were assessed with Pearson's chi-square test. Spearman rank correlation (ρ) was used to assess the association between BNP levels and clinical and echocardiographic variables. The statistical significance level of 0.05 was adopted.

Ethical considerations

This study is in accordance with the principles established in the Declaration of Helsinki, and its protocol was approved by the Ethics Committee of the Universidade Federal Fluminense (protocol 00410.258.000-08). All patients provided written informed consent.

Results

This study assessed 166 patients (mean age, 67.9 \pm 11.7 years; 72% of women), whose major clinical, echocardiographic and laboratory characteristics are shown in Table 1.

Strategy 1

The patients were divided into three groups according to their E/E' ratio values (Table 2), and were assessed according to the European Society of Cardiology Diastology Guidelines criteria, as follows: group I, patients with E/E' $>$ 15 (n = 16; 9%); group II, patients with E/E' ranging from 8 to 15 (n = 79; 48%); and group III, patients with E/E' $<$ 8 (n = 71; 43%). Group I patients had their diagnosis of HFPEF confirmed, while group III patients had the diagnosis of HFPEF excluded.

The 79 group II patients underwent analysis of other TDE parameters and ECG, and the findings were as follows: LAVI $>$ 40 mL/m² in 20 women (25%); LVMI $>$ 122 g/m² for women or $>$ 149 g/m² for men in 5 patients (6%); E/A ratio $<$ 0.5 with DT $>$ 280 ms not found in any patient; and atrial fibrillation on ECG of 2 patients (15%). Those findings allowed to diagnose HFPEF in 33 patients (42%) and to exclude it in 46 (58%) (Figure 1).

Table 1 – Epidemiological, clinical, laboratory and Doppler echocardiographic characteristics of patients

Characteristics	Total population n = 166
Age (years)	67.9 ± 11.7
Female sex (%)	72
NYHA FC II (%)	96
BMI (kg/m ²)	29.4 ± 5.9
SBP (mm Hg)	153.6 ± 26.4
HR (bpm)	77.2 ± 16.5
SAH (%)	90
Atrial fibrillation (%)	10
Diabetes (%)	28
Obesity (%)	40
Medication	
Diuretics (%)	51
BB (%)	37
ACEI/ARB (%)	67
CCB (%)	25
Biochemistry	
BNP (pg/mL)	63.5 ± 86.2
GFR (mL/min)	86.8 ± 40.1
Hemoglobin (g/dL)	13.6 ± 1.4
Echocardiography	
LVEF (%)	72.8 ± 8.1
S' cm/s	8.8 ± 2.4
LVMI g/m ²	90.5 ± 24.3
LAVI mL/m ²	33.5 ± 11.9
E' cm/s	8.8 ± 2.7
E/E' ratio	9.6 ± 4.8
E/A ratio*	0.90 ± 0.47
DT ms*	255.3 ± 80.0

* Parameters assessed in 122 patients.

NYHA FC: New York Heart Association functional class; BMI: body mass index; SBP: systolic blood pressure; HR: heart rate; SAH: systemic arterial hypertension; BB: beta-blocker; ACEI: angiotensin-converting-enzyme inhibitor; ARB: angiotensin receptor blocker; CCB: calcium channel blocker; BNP: B-type natriuretic peptide; GFR: glomerular filtration rate; LVEF: left ventricular ejection fraction; LVMI: left ventricular mass index; LAVI: left atrial volume index; DT: E-wave deceleration time; E: initial transmitral flow; A: late transmitral flow; E': myocardial relaxation velocity at the beginning of diastole; S': .

By using S 1, 49 patients with HFPEF (29% of the total sample) were identified.

Strategy 2

The patients were divided into three groups based on their BNP levels (Table 3), and BNP, TDE and ECG data were assessed according to the European Society of Cardiology Diastology Guidelines criteria. In group I (BNP > 200 pg/mL,

n = 12), HFPEF was confirmed in 12 patients (100%), 4 of whom (33%) had E/E' < 8, but LAVI > 40 mL/m², confirming the diagnosis of HFPEF (Figure 2).

In group II (BNP between 100 and 200 pg/mL, n = 20), patients with LAVI > 29 mL/m², or LVMI ≥ 96 g/m² for women or ≥ 116 g/m² for men, or E/E' ≥ 8 or atrial fibrillation on ECG were reassessed, the diagnosis of HFPEF being confirmed in 15 (75%) (Figure 2).

In group III (BNP < 100 pg/mL, n = 134), by using the European Society of Cardiology Diastology Guidelines criteria to exclude HFPEF and the same parameters already cited for group II, the patients were reassessed, and the diagnosis of HFPEF was confirmed in 26 (19%).

When BNP levels were applied to S2, HFPEF was identified in 53 patients (32% of the total sample), corresponding to 4 more patients diagnosed with HFPEF (8%) as compared with the results obtained in S1.

The mean BNP value in patients with HFPEF was 137.04 ± 113.5 pg/mL. Of the TDE parameters assessed, only LAVI showed a direct correlation with BNP levels (Table 4).

Comparing patients with HFPEF and those with non-confirmed HFPEF, a higher mean BNP level was observed in those with HFPEF (137.04 ± 113.5 vs. 29.1 ± 35.1 pg/mL; p < 0.0001).

Discussion

This study assessed two strategies derived from the European Society of Cardiology Diastology Guidelines⁹ for ambulatory patients with clinical suspicion of HFPEF, and showed that the strategy combining BNP levels and TDE findings increased HFPEF detection by 8%. Rather than having an established diagnosis of HF, the patients included in this study were suspected of having HF syndrome with an ejection fraction > 50%. Studies carried out in the community have shown that the isolate use of signs and symptoms to confirm HFPEF is difficult. Differently from patients with acute HFPEF at the emergency room, who have signs and symptoms of pulmonary and systemic congestion, ambulatory patients frequently have no signs of congestion^{9,11}.

Strategy 1

The use of the E/E' ratio in the European Society of Cardiology Diastology Guidelines for the diagnosis of HFPEF has been supported by studies with invasive methods to measure left ventricular filling pressures^{12,13} (considered gold-standard). Such methods have shown the excellent correlation of the E/E' ratio, but, by being invasive, they cannot be reproduced in ambulatory patients, which limits their assessment. The study by Emery et al¹⁴ has retrospectively assessed 1,229 consecutive TDE for the utility of measures, such as LAVI, LVMI, and pulmonary venous and mitral inflow Doppler, and has used the E/E' ratio as the major marker of dysfunction diastolic. Those authors have concluded that there was little incremental value of pulmonary flow and mitral Doppler measures, while LAVI ≥ 40 mL/m² maximized both sensitivity and specificity for the diagnosis of diastolic dysfunction. That study has shown a weak correlation between transmitral flow (E/A ratio) and E/E' ratio¹⁴.

Table 2 – Relationship of the three cutoff points of the E/E' ratio with Doppler echocardiographic parameters and atrial fibrillation

E/E' ratio	LAVI > 40 mL/m ² *		LVMI > 122 g/m ² (women) and > 149 g/m ² (men)		E/A ratio < 0.5 and DT > 280 ms**		ECG with atrial fibrillation	
	Yes	No	Yes	No	Yes	No	Yes	No
< 8 (n = 71)	9 (13%)	62	4 (6%)	67	6 (9%)	59	3 (4%)	68
8-15 (n = 79)	20 (26%)	58	5 (6%)	74	0 (0%)	66	12 (15%)	67
> 15 (n = 16)	8 (50%)	8	3 (20%)	13	0 (0%)	13	2 (12%)	14
Total	37	128	12	154	6	138	17	149

* 1 loss; ** 17 patients with atrial fibrillation. LAVI: left atrial volume index; LVMI: left ventricular mass index; DT: E-wave deceleration time; ECG: electrocardiography.

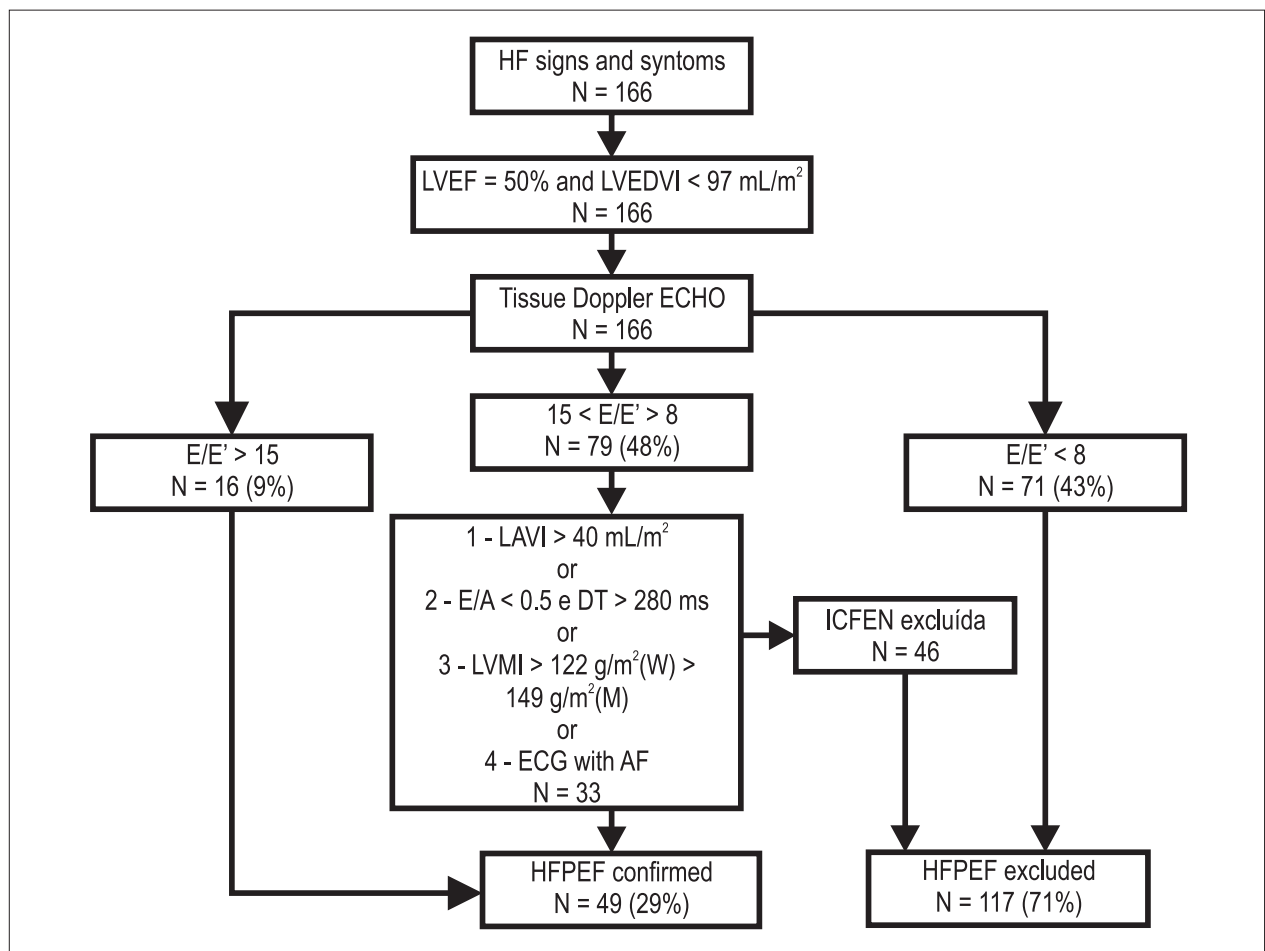


Figure 1 – Strategy 1.

HF: heart failure; LVEF: left ventricular ejection fraction; LVEDVI: left ventricular end-diastolic volume index; LAVI: left atrial volume index; DT: E-wave deceleration time; LVMI: left ventricular mass index; W: women; M: men; ECG: electrocardiography; AF: atrial fibrillation; HFPEF: heart failure with preserved ejection fraction; ECHO: echocardiography.

In our study, the percentage of patients with LAVI ≥ 40 mL/m² increased linearly with the E/E' ratio, reaching 50% when E/E' > 15. The E/A ratio showed no association with the E/E' ratio (Table 2). Those results are similar to those of the study by Emery et al¹⁴ and emphasize the non-recommendation of that parameter isolated to confirm diastolic dysfunction in patients suspected of having HFPEF, despite its wide use in clinical practice.

Strategy 2

In S2, the initial use of BNP confirmed the diagnosis of HFPEF in 53 patients (32%).

Our data showed increased BNP levels in patients with HFPEF; such values, however, were lower (137.04 ± 113.5 pg/mL) than those of patients at the emergency room. The European Society

Table 3 – Relationship of the three cutoff points of B-type natriuretic peptide (BNP) with Doppler echocardiographic parameters and atrial fibrillation

BNP	LAVI > 29 mL/m ² *		LVMI ≥ 96 g/m ² (women) and ≥ 116 g/m ² (men)		E/E' ratio ≥ 8		ECG with atrial fibrillation	
	Yes	No	Yes	No	Yes	No	Yes	No
> 200 pg/mL (n = 12)	12 (100%)	0	3 (25%)	9	8 (67%)	4	4 (33%)	8
100-200 pg/mL (n = 20)	16 (80%)	4	7 (35%)	13	16 (80%)	4	4 (20%)	16
< 100 pg/mL (n = 134)	76 (57%)	57	44 (33%)	90	71 (53%)	63	9 (7%)	125
Total	104	61	54	112	95	71	17	149

* 1 loss. LAVI: left atrial volume index; LVMI: left ventricular mass index; ECG: electrocardiography.

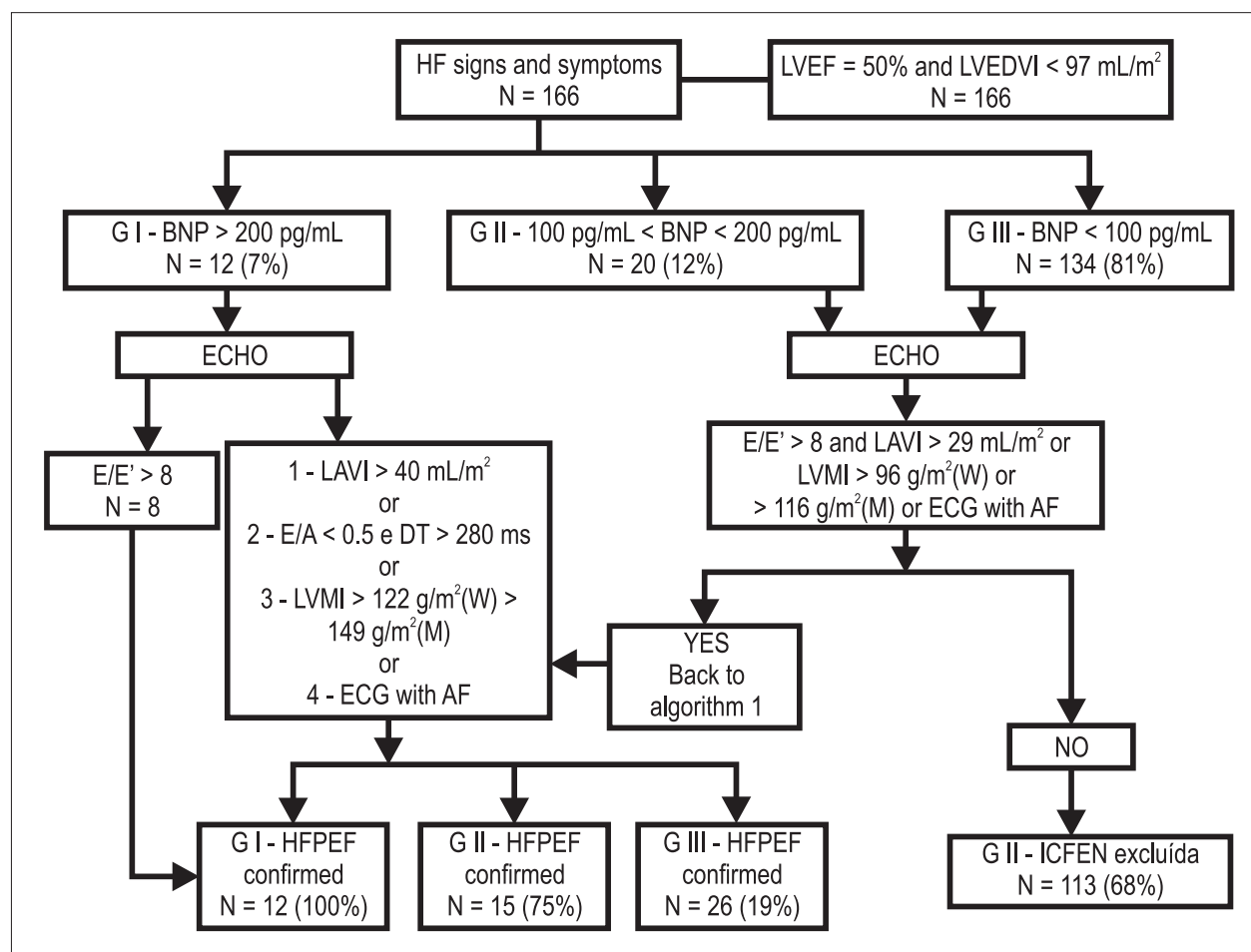


Figure 2 – Strategy 2.

HF: heart failure; LVEF: left ventricular ejection fraction; LVEDVI: left ventricular end-diastolic volume index; BNP: B-type natriuretic peptide; LAVI: left atrial volume index; DT: E-wave deceleration time; LVMI: left ventricular mass index; W: women; M: men; ECG: electrocardiography; AF: atrial fibrillation; HFPEF: heart failure with preserved ejection fraction; ECHO: echocardiography.

of Cardiology Diastology Guidelines has used the BNP cutoff point of 200 pg/mL to confirm HFPEF based on data from a study assessing patients with acute HF at the emergency room¹⁵.

Recently, Andrea et al¹⁶ have used the European Society of Cardiology Diastology Guidelines criteria to assess HF in primary-care patients in Spain. In 146 patients with signs and

symptoms of HF, the syndrome was confirmed in 65.7%, and, of those, 67% had HFPEF with a mean BNP value of 153.3 ± 123.1 pg/mL. That mean BNP value is similar to the one found in our study, confirming that BNP cutoff points for the diagnosis of HFPEF in the outpatient clinic are lower than those observed in studies performed with in-hospital patients.

Table 4 – Correlation between B-type natriuretic peptide (BNP) and Doppler echocardiographic parameters

	Pearson	p value
E/E' ratio	0.318	< 0.0001
LAVI (mL/m ²)	0.631	< 0.0001
E/A ratio	0.115	0.164
LVMI (g/m ²)	0.078	0.320

E: initial transmitral flow; E': myocardial relaxation velocity at the beginning of diastole; A: late transmitral flow; LAVI: left atrial volume index; LVMI: left ventricular mass index.

The European Society of Cardiology Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure recommends the routine measurement of natriuretic peptides in patients suspected of having HF. Those guidelines establish the BNP cutoff point of 35 pg/mL for ambulatory patients to exclude both HFPEF and HF with reduced ejection fraction (HFREF)¹⁷.

In our study, HFPEF could be found by use of TDE parameters in 20% of the patients whose BNP levels ranged from 35 to 100 pg/mL, which makes TDE indispensable in that group of patients.

The comparison between BNP levels and the TDE parameters used to diagnose HFPEF evidenced a positive association between BNP increase and LAVI (Table 4); in addition, all patients with BNP levels > 200 pg/mL had increased LAVI, which confirmed the diagnosis of HFPEF.

Four patients (2.5%) had an E/E' ratio < 8, which would exclude the diagnosis of HFPEF, but their BNP level > 200 pg/mL and LAVI > 40 mL/m² confirmed the diagnosis.

The classical diagnosis of HF is based on the presence of symptoms and signs of HF in association with cardiac structural or functional abnormalities usually demonstrated on Doppler echocardiography. That concept, however, has diagnostic difficulties for patients with HFPEF, who have mainly diastolic dysfunction¹⁷.

In epidemiological studies, the prevalence of HFPEF can range from 13% to 75% of the HF cases, depending on the diagnostic criteria used. There is great diversity in the criteria used to determine the presence of HF, in the populations studied and in the methods evaluating left ventricular function. This hinders their use in clinical practice, and because patients with HFPEF do not meet the classical definition of HF, they end up neglected and poorly assessed¹⁸.

The use of BNP measurements in association with TDE and ECG data, as shown in this study, can be a good option to confirm the diagnosis of HFPEF in ambulatory patients, considering that the BNP levels are consistently increased in patients with symptoms of HF and BNP is an excellent marker of diastolic dysfunction¹⁹.

Limitations

This study has limitations related to its sample size. In addition, no data on the difference of the Ar wave (retrograde blood flow into the pulmonary veins) and the A wave (forward transmitral flow) [(Ard – Ad)] were provided, because of the technical difficulties for obtaining that parameter (less than 50% of the patients), as already reported in other studies^{13,19}.

Conclusion

This study assessed two strategies for the diagnosis of heart failure with preserved ejection fraction, or its exclusion, based on algorithms established by the European Society of Cardiology Diastology Guidelines. This study showed that the association of B-type natriuretic peptide measurement and tissue Doppler echocardiography data is better than the use of those parameters isolated. B-type natriuretic peptide can be useful in identifying patients whose diagnosis of HF had been previously excluded based only on tissue Doppler echocardiographic findings.

Author contributions

Conception and design of the research: Jorge AJL, Ribeiro ML, Mesquita ET; Acquisition of data: Jorge AJL, Ribeiro ML, Fernandes LCM, Freire MD; Analysis and interpretation of the data: Jorge AJL, Rosa MLG, Ribeiro ML; Statistical analysis: Rosa MLG; Writing of the manuscript: Jorge AJL, Correia DS, Teixeira PD, Mesquita ET; Critical revision of the manuscript for intellectual content: Jorge AJL, Rosa MLG, Mesquita ET.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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