Original article

Diagnostic value of left atrial compliance in determining heart failure with preserved ejection fraction

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Received 19 August 2024, Revised 23 September 2024, Accepted 21 October 2024

Abstract: *Objective* — To study the diagnostic value of left atrial (LA) compliance using transthoracic echocardiogram (TTE) at rest in determining of the heart failure with preserved ejection fraction (HFpEF) depending on the result of diastolic stress test (DST).
Materials and Methods — We examined 200 patients (46.5% men, 66.0±5.8 years of age). Patients with elevated left ventricular (LV) filling pressure according to TTE at rest constituted Group I (n=34). Patients with impaired diastolic reserve according to DST constituted Group II (n=68); patients without HFpEF were placed in Group III (n=98). Speckle tracking echocardiography was used to assess left atrial reservoir strain (LASr).
Results — The groups were similar in terms of key clinical characteristics, with the exception of coronary artery disease (79.4% vs. 86.8% vs. 66.7%, respectively, p=0.011) and NYHA heart failure class (2.0±0.6 vs. 1.9±0.4 vs. 1.7±0.6; p=0.002). Statistically significant differences were also found in NT-proBNP (500.0 [261.3;817.0] pg/ml vs. 256.7 [93.9;456.3] pg/ml vs. 183.8 [60.1;310.4] pg/ml, p<0.001) and both pre-test scoring scales, HFA-PEFF (6.0 [5.0;6.0] vs. 5.0 [4.0;6.0] vs. 4.0 [3.0;5.0], p<0.001) and H2FPEF (5.0 [3.0;6.0] vs. 5.0 [3.0;5.0] vs. 4.0 [3.0;5.0], p=0.001). Statistically significant differences between Groups I and II and Groups I and III were detected for most echocardiographic parameters. No significant differences were found between Groups II and III, except for the following parameters: E/e' (11.2 [9.8; 12.6] vs. 9.3 [7.7; 10.9], respectively, p<0.001), LASr (21.4 [19.8; 24.5] % vs. 27.6 [24.6; 29.8] %, p < 0.001) and LA compliance (2.0 [1.6; 2.4] vs. 3.0 [2.4; 3.7], p<0.001). According to ROC analysis, the largest area under the curve (AUC), as well as optimal sensitivity and specificity in determining HFpEF in Groups II and III, were observed for LA compliance (AUC=0.837, p<0.001; 76.5% and 76.5%). Lower classification quality was demonstrated by the left atrial volume index (LAVI)/LASr (AUC=0.720, p<0.001; 69.1% and 62.2%), H2FPEF scale (AUC=0.629, p=0.006; 60.3% and 65.3%), NT-proBNP (AUC=0.615, p=0.014; 60.0% and 58.1%), and HFA-PEFF score (AUC=0.610, p=0.019; 60.3 and 54.1%).
Conclusion — LA compliance with the cutoff point <2.4 has the highest ability to detect HFpEF depending on the DST result among all pre-test diagnostic tools.

Keywords: heart failure with preserved ejection fraction, speckle tracking echocardiography, left atrial strain, diastolic stress test, supine bicycle stress echocardiography.

Cite as Shirokov NE, Yaroslavskaya EI, Krinochkin DV, Kosterin MD, Musikhina NA. Diagnostic value of left atrial compliance in determining heart failure with preserved ejection fraction. *Russian Open Medical Journal* 2024; 13: e0409.

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Introduction

Heart failure with preserved ejection fraction (HFpEF) is characterized by a combination of diastolic dysfunction (DD) and high left ventricular (LV) filling pressure, clinically manifested by dyspnea [1]. Conventional transthoracic echocardiogram (TTE) at rest is sufficient to diagnose HFpEF with more pronounced DD and concomitant remodeling of the left heart chambers [2]. Such patients complain of dyspnea during mild physical exertion (PE). However, many patients experience dyspnea during moderate PE. Therefore, such patients are recommended to undergo a diastolic stress test (DST), which allows modeling the conditions for the occurrence of dyspnea and assessing diastolic reserve [2, 3].

On the other hand, attempts were made to develop an alternative to DST [4]. There are valid tools for pre-test diagnostics of HFpEF, such as the 2018 H2FPEF clinical and instrumental scale, and the 2019 HFA-PEFF instrumental and laboratory algorithm. However, the results of their application have low consistency with each other [5]. The updated British Society of Echocardiography Guidelines for the Assessment of LV Diastolic Function (2024) was the first to propose using left atrial reservoir strain (LASr) by TTE at rest to determine HFpEF [6].

The phases of the cardiac cycle determine the functions of the left atrium (LA), which are largely independent of the LA per se [7]. Thus, during LV contraction, the LA serves as a reservoir for the pulmonary venous flow. At normal LA mean pressure, most of its filling occurs during the reservoir phase. However, as LV filling pressure and mean LA pressure increase, LA filling shifts to the next conduit phase [7]. Therefore, LA phase analysis, in particular a decrease in LASr, can be considered a key link in the modern instrumental definition of HFpEF by resting TTE [1, 6, 8]. Moreover, it seems appropriate to identify worsening of DD using LA compliance analysis (the ratio of mean LA pressure to LV filling pressure) [9].

Objective: To study the diagnostic value of LA compliance using TTE at rest in determining HFpEF depending on the DST result.

Material and Methods

Study subjects

Patients with hypertension (HTN) and comorbidities complaining of unexplained dyspnea/chest pain during PE underwent TTE at rest.

The inclusion criterion for our study was DD with decreased mitral annular velocity assessed by tissue Doppler imaging [10]. The diagnostic algorithm for assessing LV diastolic function is presented in the 2016 American Society of Echocardiography and the European Association of Cardiovascular Imaging (ASE/EACVI) guidelines [10]. The presence of two or three positive criteria out of three possible was used to conclude that there was increased LV diastolic filling at rest. The early diastolic flow peak velocity of the mitral valve (E) to early diastolic peak velocity of mitral valve annulus (e') ratio (E/e') >14, left atrial volume index (LAVI) >34 ml/m2, and tricuspid regurgitation velocity >2.8 m/s were taken into account. Otherwise, DST was performed as part of supine bicycle stress echocardiography in accordance with current recommendations [2, 3]. An increase in the mean E/e' >14 / septal E/e'>15 was employed to conclude about impaired diastolic reserve. The criterion for stress-induced ischemia was the appearance of impaired local contractility of the LV myocardium corresponding to the blood supply pool of the affected coronary artery [11, 12].

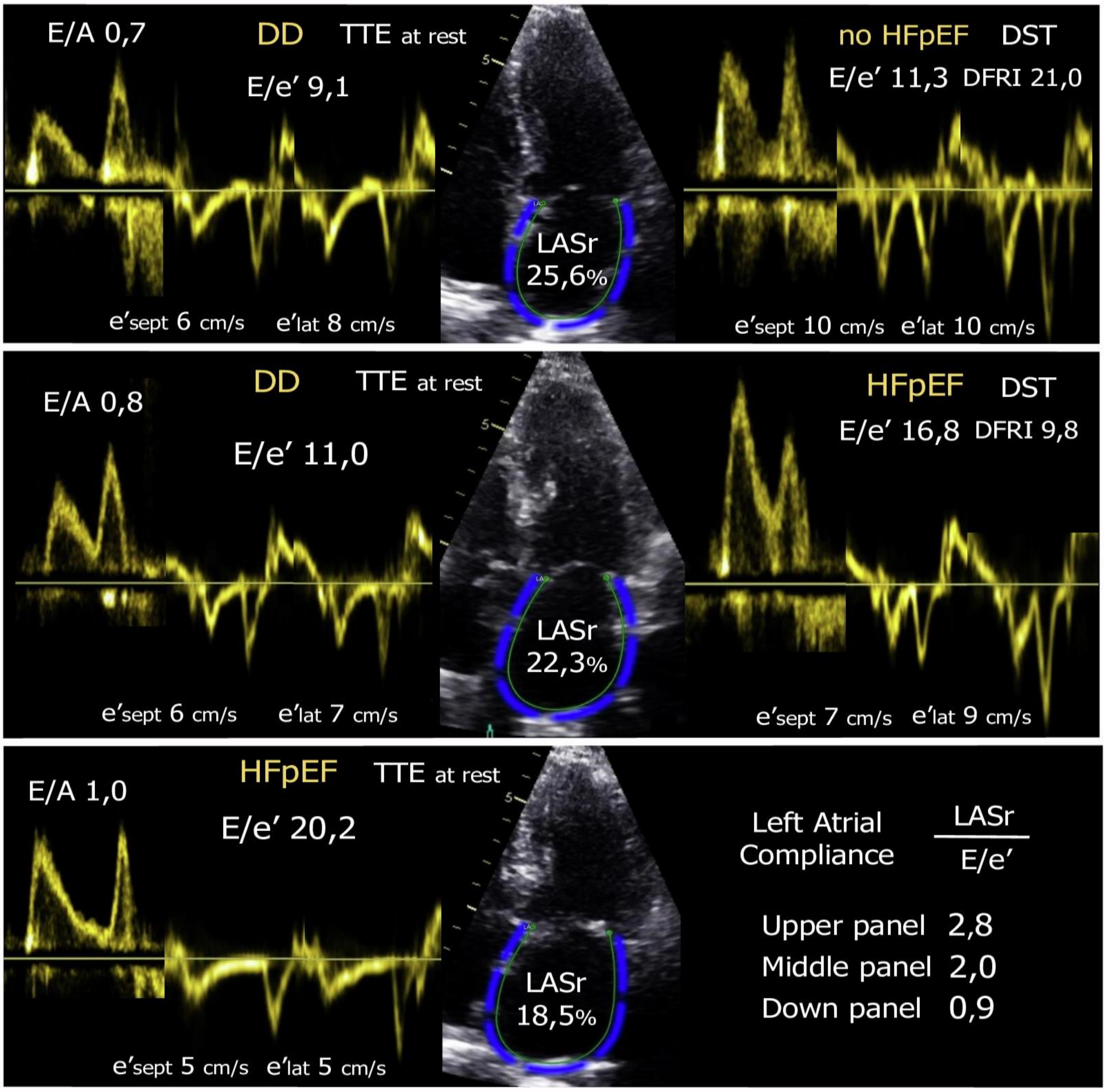

Figure 1. Variants of DD severity and HFpEF diagnostics. Upper panel: baseline DD (Grade 1, impaired LV relaxation), LASr above reference value (≥24.0%), normal LA compliance, normal diastolic reserve according to DST (no HFpEF). Middle panel: baseline DD (Grade 1, impaired LV relaxation), decreased LASr, decreased LA compliance, impaired diastolic reserve according to DST (HFpEF). Lower panel: DD with high LV filling pressure at rest (Grade 2, pseudonormal), DST is not required (HFpEF).

Table 1. Clinical characteristics of study subjects (n=200)

Parameter		*Group I (n=34)*	*Group II (n=68)*	*Group III (n=98)*	*P1*	*P2*	*P3*	*P4*
		HFpEF (n=102)		No HFpEF (DD only)	*(All groups)*	*(Groups I and II)*	*(Groups II and III)*	*(Groups I and III)*
Age, years		66.1±6.3	66.6±4.9	65.3±6.1	0.327	-	-	-
Gender: male, %		32.4	41.2	55.1	0.087	-	-	-
BMI, kg/m2		32.0 [28.8; 34.7]	32.2 [28.4; 36.0]	30.3 [27.7; 32.7]	0.060	-	-	-
Obesity, %		55.9	63.2	53.6	0.461	-	-	-
HTN, %		100.0	100.0	100.0	0.593	-	-	-
HTN grade	I	0.0	0.0	10.2	0.051	-	-	-
	II	17.6	8.8	16.3				
	III	82.4	91.2	73.5				
CAD, %		79.4	86.8	66.7	0.011	0.391	0.005	0.194
Angina pectoris, NYHA class	I	3.0	16.7	10.8	0.074	-	-	-
	II	48.5	59.1	45.2				
	III	9.1	3.0	2.2				
MI, %		14.7	16.2	15.3	0.979	-	-	-
PCI, %		20.6	26.5	18.6	0.472	-	-	-
Paroxysmal AF, %		27.3	15.2	14.9	0.234	-	-	-
DM, %		52.9	35.3	33.3	0.116	-	-	-
Heart failure, NYHA class	I	15.2	10.6	34.1	0.002	0.597	0.003	0.004
	II	69.7	86.4	61.7				
	III	15.1	3.0	4.2				
6MWT, m		390.5 [310.5; 410.0]	410.0 [380.0; 456.0]	415.0 [360.0; 452.5]	0.037	0.060	0.457	0.031
NT-proBNP, pg/ml		500.0 [261.3; 817.0]	256.7 [93.9; 456.3]	183.8 [60.1; 310.4]	<0.001	0.007	0.019	<0.001
HFA-PEFF, %		6.0 [5.0; 6.0]	5.0 [4.0; 6.0]	4.0 [3.0; 5.0]	<0.001	0.002	0.016	<0.001
H2FPEF, %		5.0 [3.0; 6.0]	5.0 [3.0; 5.0]	4.0 [3.0; 5.0]	0.001	0.498	0.003	0.002

AF, atrial fibrillation; HTN, hypertension; BMI, body mass index; CAD, coronary artery disease; DM, diabetes mellitus; NYHA, New York Heart Association; MI, myocardial infarction; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; PCI, percutaneous coronary intervention, 6MWT, six-minute walk test.

Table 2. Pharmacotherapy of study subjects (n=200)

Parameter	*Group I (n=34)*	*Group II (n=68)*	*Group III (n=98)*	*P1*	*P2*	*P3*	*P4*
	HFpEF (n=102)		No HFpEF (DD only)	*(All groups)*	*(Groups I and II)*	*(Groups II and III)*	*(Groups I and III)*
β-blockers	67.6	77.9	52.0	0.009	0.998	0.003	0.540
ACE inhibitors	23.5	32.4	32.7	0.999	-	-	-
ARBs	61.8	58.8	56.1	0.999	-	-	-
MRA	17.6	7.4	9.3	0.747	-	-	-
Diuretics	50.0	44.1	37.8	0.999	-	-	-
CCBs	35.3	36.8	30.6	0.999	-	-	-
Antiplatelet drugs	50.0	58.8	40.8	0.072	-	-	-
Anticoagulants	20.6	17.6	11.2	0.946	-	-	-
Statins	61.8	83.8	65.3	0.045	0.072	0.036	0.998
AAD	17.6	10.3	7.1	0.636	-	-	-
SGLT2 inhibitors	14.7	16.4	8.2	0.729	-	-	-

AAD, antiarrhythmic drugs; MRA, mineralocorticoid receptor antagonists; CCBs, calcium channel blockers; ARBs, angiotensin II receptor blockers; ACE, angiotensin-converting enzyme; SGLT2, sodium/glucose cotransporter 2.

The exclusion criteria for the study were as follows: hemodynamically significant congenital/acquired valvular heart disease; peripheral arterial disease of the lower extremities; phlebitis/deep vein thrombosis of the lower extremities; inability to achieve a heart rate (HR) sufficient to complete the DST.

The study protocol was approved by the local ethics committee. Informed consent was obtained from each patient included in the study.

A total of 200 patients (46.5% men, 66.0±5.8 years of age) were examined. Patients with elevated LV filling pressure according to resting TTE constituted Group I (n=34, HFpEF diagnosed at rest). Patients with impaired diastolic reserve according to DST constituted Group II (n=68, HFpEF diagnosed by supine bicycle stress echocardiography); patients with normal diastolic reserve according to DST constituted Group III (n=98, HFpEF excluded based on supine bicycle stress echocardiography result) (*Figure 1*).

Analyzing echocardiography

Echocardiography was performed using a General Electric (GE) Vivid E9 expert-class ultrasound system and an M5Sc-D matrix transducer (1.5-4.6 MHz). Data were stored in DICOM format. Image and digital cine-loop analysis were performed on an IntelliSpace Cardiovascular workstation, ToMTec platform (Philips, USA) in compliance with current recommendations [13]. Speckle tracking echocardiography was used to assess LASr and LV global longitudinal strain (GLS) [13, 14].

Supine bicycle stress echocardiography was performed using a GE eBike ergometer (USA). Steps with a power of 25 W in conditions of PE increasing every two minutes were used to achieve the target HR (85% of maximum/until symptoms occurred, preventing continuation of the stress test). The cadence was 60 rpm.

Table 3. Transthoracic echocardiogram parameters in study subjects (n=200)

Parameter	*Group I (n=34)*	*Group II (n=68)*	*Group III (n=98)*	*P1*	*P2*	*P3*	*P4*
	HFpEF (n=102)		No HFpEF (DD only)	*(All groups)*	*(Groups I and II)*	*(Groups II and III)*	*(Groups I and III)*
			Morphological status				
IVS, mm	13.5 [12.0; 15.0]	13.0 [12.0; 13.8]	12.0 [11.0; 14.0]	0.057	-	-	-
LV posterior wall, mm	12.0 [10.0; 13.0]	11.0 [10.0; 12.0]	11.0 [10.0; 12.0]	0.057	-	-	-
LV MMI, g/m2	127.6 [107.4; 146.5]	115.4 [104.4; 130.7]	110.4 [95.2; 126.3]	0.004	0.177	0.036	0.002
LV EDV, ml	72.0 [68.5; 82.0]	80.0 [70.0; 92,5]	83.0 [72.0; 96.0]	0.022	0.038	0.472	0.006
LA volume, ml	73.0 [64.5; 87.0]	63.5 [52.0; 71.0]	58.0 [49.8; 68.0]	<0.001	<0.001	0.144	<0.001
LAVI, ml/m2	40.4 [37.2; 44.0]	32.0 [28.3; 38.0]	30.1 [26.0; 35.3]	<0.001	<0.001	0.050	<0.001
LA diameter, mm	42.0 [40.0; 46.0]	40.5 [38.0; 43.0]	39.0 [37.0; 42.0]	0.001	0.041	0.046	<0.001
LA enlargement, %	85.3	42.6	33.7	<0.001	<0.001	0.257	<0.001
RA volume, ml	44.5 [39.0; 53.3]	40.0 [34.3; 49.8]	40.0 [34.0; 49.3]	0.126	-	-	-
RV diameter, mm	28.0 [26.0; 29.3]	28.0 [26.0; 30.0]	28.0 [26.0; 30.0]	0.839	-	-	-
			Functional status				
LVEF, %	67.0 [65.0; 70.0]	66.0 [64.0; 68.0]	66.0 [63.0; 68.0]	0.147	-	-	-
sPAP, mmHg	25.5 [20.8; 32.0]	25.0 [20.0; 29.0]	23.0 [18.0; 27.0]	0.014	0.379	0.270	0.015
Peak early diastolic transmitral flow velocity, cm/s	93.5 [81.0; 107.8]	68.0 [61.0; 80.8]	57.5 [48.8; 67.3]	<0.001	<0.001	<0.001	<0.001
Peak late diastolic transmitral flow velocity, cm/s	91.0 [57.5; 112.5]	89.5 [79.0; 101.0]	80.5 [70.0; 95.3]	0.050	-	-	-
E/A ratio	1.0 [0.8; 1.5]	0.8 [0.6; 0.9]	0.7 [0.6; 0.8]	<0.001	<0.001	0.123	<0.001
TDI e’, IVS, cm/s	5.0 [4.0; 6.0]	5.0 [5.0; 6.0]	5,0 [5.0; 6.0]	0.268	-	-	-
TDI e’, LV lateral wall, cm/s	6.0 [5.0; 7.0]	7.0 [6.0; 8.0]	8.0 [6.0; 8.0]	0.001	0.022	0.075	<0.001
Mean E/e’ ratio	16.2 [14.9; 19.5]	11.2 [9.8; 12.6]	9.3 [7.7; 10.9]	<0.001	<0.001	<0.001	<0.001
GLS, %	18.5 [14.9; 20.5]	18.3 [16.3; 19.9]	18.4 [16.8; 20.7]	0.268	-	-	-
GLS decrease <-18%, %	44.8	38.2	39.1	0.998	-	-	-
LASr, %	15.5 [11.6; 18.2]	21.4 [19.8; 24.5]	27.6 [24.6; 29.8]	<0.001	<0.001	<0.001	<0.001
LASr decrease <24%, %	97.1	69.1	23.5	<0.001	0.002	<0.001	<0.001
LAScd, %	7.6 [5.3; 10.0]	9.8 [7.8; 11.6]	9.9 [7.2; 13.0]	<0.001	<0.001	0.871	0.001
LASct, %	7.5 [4.9; 10.7]	11.7 [9.0; 14.6]	17.0 [13.6; 20.1]	0.001	0.002	0.001	0.001
LA compliance	0.9 [0.7; 1.1]	2.0 [1.6; 2.4]	3.0 [2.4; 3.7]	<0.001	<0.001	<0.001	<0.001
LA compliance <2.4, %	100.0	78.0	24.5	0.001	0.002	<0.001	<0.001
LAVI / LASr	2.5 [2.2; 3.6]	1.5 [1.2; 2.0]	1.1 [0.9; 1.4]	<0.001	<0.001	<0.001	<0.001

PW, posterior wall; LV, left ventricle; LA, left atrium; EDV, end-diastolic volume; LVEF, left ventricular ejection fraction; sPAP, systolic pulmonary artery pressure; MMI, myocardial mass index; IVS, interventricular septum; EF, ejection fraction; LA, left atrium; LAScd, left atrium conduit strain; LASct, left atrial contraction strain; LASr, left atrial reservoir strain; GLS, global longitudinal strain; RV, right ventricle; RA, right atrium; LAVI, left atrial volume index.

Table 4. supine bicycle stress echocardiography results (n=166)

Parameter	*Group II (n=68)*	*Group III (n=98)*	*P (Groups II and III)*
	Functional status (physical exertion)		
Peak E, cm/s	123.0 [109.0;132.0]	91.5 [74.0; 110.5]	<0.001
TDI e’, IVS, cm/s	7.0 [7.0;8.0]	9.0 [7.0;10.0]	<0.001
TDI e’, LV lateral wall, cm/s	9.0 [8.0;10.0]	11.5 [10.0;13.0]	<0.001
Mean E/e’ ratio	14.7 [13.8;15.5]	9.4 [7.9;10.5]	<0.001
Septal E/e’ ratio	16.8 [15.0;17.8]	10.5 [9.1;12.4]	<0.001
DFRI	11.3 [6.8;15.0]	22.5 [15.0;29.3]	<0.001
TR, mmHg	34.5 [23.0;45.0]	30.0 [21.0;40.0]	0.049
TR≥40, mmHg, %	45.6	27.6	0.013
Stress-induced ischemia, %	8.8	11.2	0.410
	Physical status		
Exercise tolerance, W	75.0 [50.0;75.0]	100.0 [75.0;100.0]	<0.001
Stress test duration, min	6.0 [5.0;7.0]	7.0 [6.0;8.0]	<0.001
Maximum heart rate, bpm	100.5 [95.3;107.8]	108.0 [96.0;116.0]	0.002
Shortness of breath as a reason for stopping the test, %	73.5	13.3	<0.001

TDI, tissue Doppler imaging; IVS, interventricular septum; LV, left ventricle; DFRI, diastolic functional reserve index; TR, tricuspid regurgitation.

Laboratory data

Laboratory examination included blood biochemistry test. The level of N-terminal prohormone of brain natriuretic peptide (NT-proBNP) was determined by solid-phase chemiluminescent enzyme immunoassay on the ALISEI Q.S. analyzer (Next Level Strumenti Diagnostici, Italy).

Statistical data processing

Statistical analysis was performed using the IBM SPSS Statistics 26 software for social studies. The Kolmogorov-Smirnov test was employed to determine the normality of distribution.

For two unrelated groups, we used Student’s t-test to compare quantitative variables in case of their normal distribution; the results are presented as M±SD (M: mean; SD: standard deviation). The Mann-Whitney U test was used to analyze quantitative variables with a distribution other than normal; the results are presented as the median with the interquartile range (25th and 75th percentiles). Qualitative variables were compared using the Pearson's chi-squared test.

To analyze the quantitative values of the three unrelated groups with their normal distribution, we employed one-way analysis of variance (ANOVA) with Bonferroni correction. To evaluate the quantitative variables following a distribution different from normal, the Kruskal-Wallis test with corrections for multiple comparisons was used.

Spearman's correlation analysis was performed to determine the expression of relationships. Logistic regression analysis was employed to identify an independent relationship. ROC analysis was used to evaluate and compare diagnostic methods. The optimal cutoff point was determined by constructing the ROC curve. The difference was considered statistically significant at $p<0.05$.

Results

The values of clinical, functional and instrumental parameters of patients are presented in *Tables 1-5*.

Groups were comparable in terms of key clinical parameters, except for the presence of coronary artery disease (CAD) and heart failure class according to the New York Heart Association (NYHA) (*Table 1*). Also, we observed statistically significant differences in the values of NT-proBNP and both pre-test scales (HFA-PEFF and H2FPEF) (*Table 1*).

We revealed no statistically significant differences between groups in the main acceptable medications with the exception of β-blockers and statins (*Table 2*).

Statistically significant differences between Groups I and II and Groups I and III were found for most echocardiographic parameters (*Table 3*). Of particular importance is the fact that there were no differences in LV contractility and size of right heart chambers. Furthermore, Groups II and III were similar in terms of key parameters, except for LASr, E/e' and LA compliance (*Table 3*).

Statistically significant differences were observed in all parameters based on supine bicycle stress echocardiography between Groups II and III, except for stress-induced ischemia (*Table 4*).

According to the Spearman's correlation analysis, correlations were revealed in groups II and III between the LA compliance according to resting TTE and septal E/e' according to DST (r=-0.444; p<0.001), and LA compliance and NT-proBNP level (r=-0.213; p=0.007) (*Figure 2*).

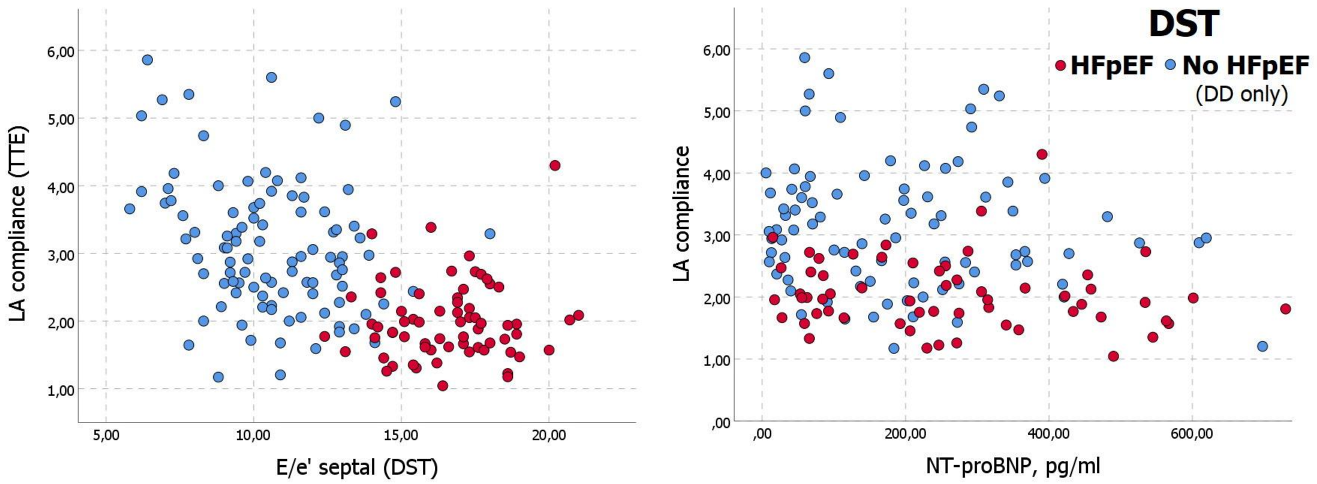

Figure 2. Correlations in Groups II and III. DD, diastolic dysfunction; DST, diastolic stress test; HFpEF, heart failure with preserved ejection fraction; LA, left atrium; NT-proBNP, N-terminal prohormone of brain natriuretic peptide.

Table 5. Diagnostic tools for determining HFpEF

Parameter	*Value*	*AUC*	*CI 95%*	*P*	*Sensitivity, %*	*Specificity, %*
Groups II vs III (DST only for HFpEF diagnostics, n=166)						
LA compliance	<2.4	0.837	0.774-0.900	<0.001	76.5	76.5
LAVI/LASr	≥1.3	0.720	0.639-0.801	<0.001	69.1	62.2
NT-proBNP, pg/ml	≥215	0.615	0.526-0.703	0.014	60.0	58.1
HFA-PEFF	≥5	0.610	0.521-0.698	0.019	60.3	54.1
H2FPEF	≥5	0.629	0.542-0.716	0.006	60.3	65.3

HFpEF, heart failure with preserved ejection fraction; LA, left atrium; LASr, left atrial reservoir strain; LAVI, left atrial volume index; NT-proBNP, N-terminal prohormone of brain natriuretic peptide.

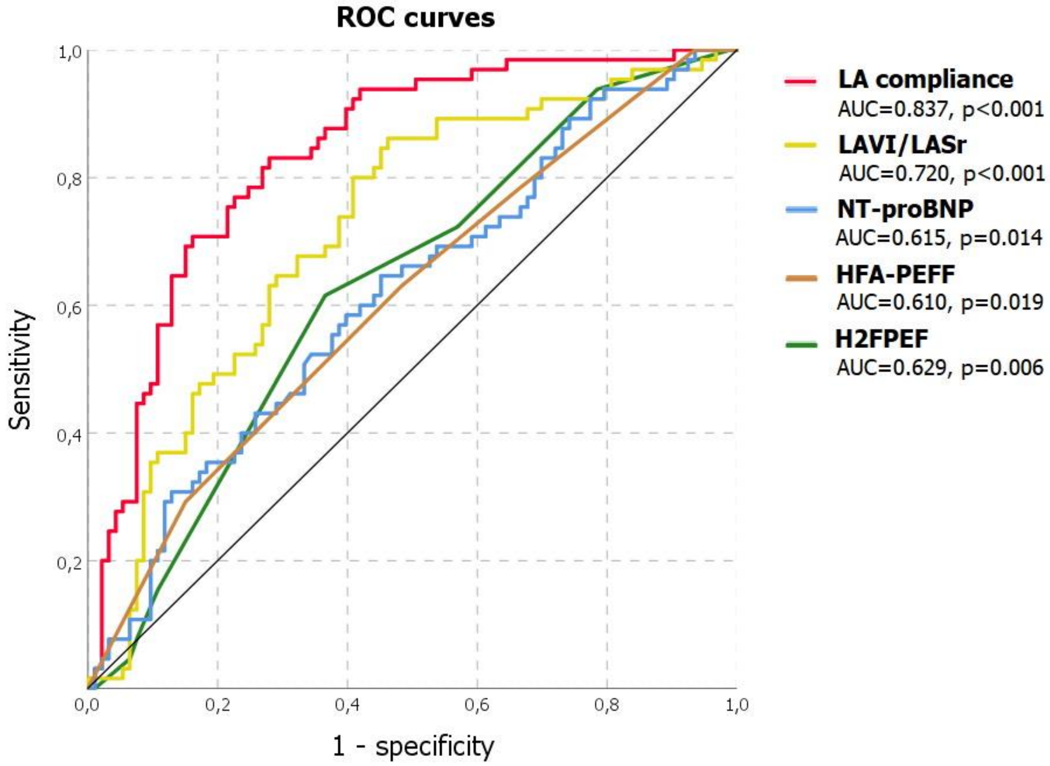

Figure 3. Sensitivity and specificity of pre-test instruments in detecting HFpEF (Groups II and III). HFpEF, heart failure with preserved ejection fraction; LA, left atrium; LASr, left atrial reservoir strain; LAVI, left atrial volume index; NT-proBNP, N-terminal pro-brain natriuretic peptide.

ROC analysis was performed to identify a tool that could be considered as an alternative to DST in determining HFpEF. Among all methods (LA compliance, LAVI/LASr, H2FPEF, HFA-PEFF, NT-proBNP), the largest area under the curve (AUC), as well as optimal values of sensitivity and specificity, were found for LA compliance with a value of <2.4 (*Figure 3*; *Table 5*). According to logistic regression data, of all pre-test diagnostic tools, only LA compliance (OR 0.155; 95% CI 0.082-0.292; p<0.001) had an independent relationship with the DST result. It is important to have data on higher specificity for LA compliance (value <2.2: sensitivity 72.1% and specificity 82.7%, p<0.001; value <2.0: sensitivity 58.8% and specificity 88.8%, p<0.001).

Discussion

The authors of the H2FPEF scale consider obesity the dominant cause of HFpEF [15]. Obesity is a pandemic of the 21st century, as the disease is extremely widespread and contributes to many pathologies including the cardiovascular system [16]. However, according to our data, about half of patients with HFpEF suffered from it. Obesity is accompanied by systemic chronic immune inflammation of low intensity (meta-inflammation) [17]. It is also known that persistent increase in systemic arterial pressure enhances proinflammatory and profibrotic signaling pathways [18, 19]. According to our data, all patients with DD had HTN. On the other hand, of all clinical characteristics, only CAD was statistically significantly more common in HFpEF. Given the similar rates of MI, PCI, and stress-induced ischemia, the incidence of CAD in patients with HFpEF is most certainly associated with damage to large coronary arteries and the microcirculatory bed [20, 21].

Proinflammatory diseases trigger excessive levels of cytokines in the coronary microvasculature, which leads to subendothelial migration of immunocompetent cells [18]. Endothelial dysfunction is closely associated with oxidative stress and deficiency of the NO-cGMP-PKG signaling pathway [18,22]. As a result, the giant sarcomeric protein, titin, loses its extensibility. LV myocardial stiffness increases due to the disruption of the basic property of the protein, which is key for diastolic function [18]. More significant processes in the impairment and progression of HFpEF continue in the extracellular matrix (ECM) [18, 23]. Monocytes infiltrating the ECM become macrophages and produce cytokines to activate and stimulate fibroblasts. A series of reactions involving multiple signaling molecules are carried out for the synthesis and degradation of type I and type III collagen. Dysregulation of these processes results in excessive myocardial fibrosis [18, 23].

All the above processes result in myocardial stress first during PE and then at rest [2, 23]. Increased LV filling pressure due to inability of LV myocardium to stretch adequately is estimated as elevated E/e’ ratio during conventional TTE at rest [3]. Increased mean LA pressure/excessive LA wall stretch associated with higher E/e’ ratio becomes a stimulus for release of myocardial stress marker NT-proBNP by cardiomyocytes [24]. It is known that the half-life of NT-proBNP is approximately 120 min [25]. According to our data, persistently elevated NT-proBNP levels were observed only in patients with higher LV filling pressure at rest and more remodeled left heart chambers (Group I).

The increase in mean LA pressure is assessed by the decrease in LASr during performing resting TTE [4]. LA compliance (LASr to E/e’ ratio) can act as a conceptual measure of the compliance of LA and LV functions. Probably, LA compliance analysis can reveal the severity of DD characteristic of HFpEF [26, 27]. Moreover, the LAVI/LASr ratio may also be relevant in detecting HFpEF due to the relationship of morphological and functional remodeling with NT-proBNP release [28]. These parameters were worse in patients with HFpEF confirmed by supine bicycle stress echocardiography (Group II vs. Group III).

Moreover, our data suggested that the ability of LA compliance in detecting HFpEF was the highest among all pre-test tools (Group II vs. Group III). Currently, DST is mainly recommended for the diagnosis of HFpEF in such patients [29]. Indeed, timely diagnosis of HFpEF can be made by DST as impaired diastolic reserve and by resting TTE as impaired LA compliance in a less remodeled heart [30]. LA compliance may be the preferred choice for determining HFpEF in patients in whom DST cannot be performed due to comorbidities.

Conclusion

Among all pre-test diagnostic tools, LA compliance with a cut-off point of <2.4 has the greatest ability to determine HFpEF depending on the DST result.

Limitations

First and foremost, all patients enrolled in our study had diastolic dysfunction. The study had no control data collected from patients with normal diastolic function. Also, follow-up is necessary to observe and confirm the relationship between the studied instrumental parameters and clinical characteristics.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Conflict of interest

The authors declare that they have no conflicts of interest.

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