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Left Atrial Strain as a Predictor of Diastolic Stress Test Results in Patients With Arterial Hypertension

Aim To study a possibility of using the left atrial strain (LAS) for predicting results of the noninvasive diastolic stress test (DST) in patients with arterial hypertension (AH).

Material and methods The study included 98 patients previously diagnosed with AH. As a part of evaluation for complaints of dyspnea, palpitation or pain in the area of the heart, DST and transthoracic echocardiography were performed. Echocardiography included measurements of LAS in the reservoir phase, left atrial volume index (LAVI), pulmonary artery systolic pressure (PASP), and ratio of early filling transmitral flow velocity to mitral annular velocity (E/e').

Results The DST was negative in 52 patients (group 1) and positive in 46 patients (group 2). Group 2 had greater values of mean E/e' (11.0 [9.4; 12.6] vs 9.0 [7.9; 11.1], p=0.0003); LAVI (33.8 [29.0; 40.0] ml/m² vs 28.0 ml/m² [25.0; 32.9], p=0.0001); and PASP (29.0 mm Hg [28.0; 30.0] vs 26.0 mm Hg [25.0; 28.0], p<0.0001 were greater, but LAS values were lower (19.0% [18.0; 21.0] vs 24.0% [22.0; 28.0], p<0.0001. The predictive capability of LAS with respect of heart failure was higher than of other echocardiographic parameters. The area under the ROC curve (AUC) for the reservoir strain was 0.922 (95% confidence interval, CI, 0.851–0.967), which was significantly greater than for E/e': 0.713 (0.613–0.800); the LAVI was 0.724 (0.624–0.809); and the PASP was 0.764 (0.668–0.844). A LAS value in the reservoir phase less than 22% predicts a positive result of DST with a probability of 88.9% (76.5–95.2%). Higher values of the strain allow expecting a negative DST result with a probability of 88.7% (77.4–94.7%).

Conclusion If the DST cannot be performed for a noninvasive diagnosis of heart failure with preserved ejection fraction, a positive result of this test can be predicted by a decrease of LAS in the reservoir phase to 21% or lower. The diagnostic accuracy of this criterion is 88.8% (81.0–93.6%).

Keywords Chronic heart failure with preserved ejection fraction; arterial hypertension; diastolic stress test; left atrial strain

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Introduction

Heart failure with preserved ejection fraction (HFpEF) is an increase in the left ventricular (LV) filling pressure at rest or during exercise, not associated with LV systolic dysfunction. Direct measurement of the LV end-diastolic pressure or pulmonary capillary wedge pressure is the gold standard for the diagnosis of HFpEF. However, it is acceptable to use indirect signs of increased LV filling pressure for the diagnosis of HFpEF in routine clinical practice, such as elevated plasma levels of natriuretic peptides [1], early transmitral filling velocity-to-mitral annular velocity ratio (E/e') >9 [2–4], pulmonary artery systolic pressure (PASP) >35 mm Hg [2, 5], and left atrial volume index (LAVI) >34 mL/m² in sinus rhythm and >40 mL/m² in atrial fibrillation (AF) [1, 2].

Since none of these indicators can be the only criterion for the diagnosis of HFpEF [6], an integrated approach is recommended that uses several non-invasive signs of increased pressure [2]. However, even this approach allows diagnosing HFpEF in only 60% of patients since filling pressure is not increased at rest in the early stages of the disease.

One solution to this problem is the use of a non-invasive diastolic stress test (DST) for the diagnosis of HFpEF, i.e., the determination of echocardiographic signs of increased filling pressure after graduated exercise [7, 8]. The criterion for the diagnosis of HFpEF is increased E/e' ≥15 with a simultaneous increase in tricuspid regurgitation velocity ≥3.4 m/s [2, 8].

DST is a more accessible technique than invasive measurement of LV filling pressure, but its wider use is limited by two circumstances. First, DST is performed in a laboratory equipped and licensed to perform echocardiographic examinations and stress testing. Second, DST should be carried out by an expert licensed in two different specialties (ultrasound diagnostics and functional diagnostics) or two respective experts. Thus, DST is no more accessible in routine clinical practice than invasive diagnosis of HFpEF.

Recent trials have shown that left atrial (LA) reservoir strain determined by speckle tracking has a higher discriminatory power to differentiate HFpEF than other echocardiographic signs [9–12]. The Biomarkers and Imaging Study Groups of the Heart Failure Association of the European Society of Cardiology agreed that further consideration should be given to integrating LA strain into the algorithm for non-invasive diagnosis of HFpEF [13]. Given the identified challenges of conducting DST in routine clinical practice, we consider relevant to study the possibility of replacing DST with the assessment of LA strain at rest.

Objective

Study the possibility of using LA strain to predict the results of non-invasive DST in patients with arterial hypertension (AH).

Material and Methods

Observational, cross-sectional, single-center study was conducted following the Good Clinical Practice and the Declaration of Helsinki and approved by the Ethics Committee of Tver State Medical University. When being admitted to the hospital, all patients signed the informed consent using the study results for scientific purposes.

All patients with previously diagnosed AH, who underwent DST and assessment of left atrial strain indices during the examination conducted in connection with complaints of dyspnea, palpitations or chest pain, were enrolled in the study in succession.

The study did not include patients with a history of typical angina attacks, myocardial infarction, or coronary artery intervention, permanent and persistent AF. Patients without left ventricular hypertrophy (LVH) according to echocardiogram, with reduced left ventricular ejection fraction (LVEF) < 50%, or valvular heart disease, and patients with signs transient myocardial ischemia shown by 24-hour ECG monitoring or exercise stress test, were excluded from the study.

Sex and age of patients, the presence of concomitant diabetes mellitus and obesity, administration of antihypertensive drugs and BP at the time of the study were taken into consideration. Body mass index (BMI) 25,0–29,9 kg/m^2 corresponded to overweight, BMI ≥30.0 kg/m^2 was indicative of obesity. Target blood pressure level was <140/90 mm Hg.

All patients underwent transthoracic echocardiography (Vivid S70, GE, USA) to determine the LV myocardial index (LVMI), LVEF, LAVI, PASP and early transmitral filling velocity-to-mitral annular velocity ratio (E/e') [13].

LVH was diagnosed and assessed in non-obese individuals by LV mass indexed to body surface area: 116–131 g/m^2 in male patients or 96–108 g/m^2 in female patients correspond to mild LVH (grade 1), 132–148 g/m^2 or 109–121 g/m^2, respectively, to moderate LVH (grade 2), higher LVMI was indicative of severe LVH (grade 3). In obese individuals, mass was indexed to height: 49–55 g/m$^{2.7}$ in male patients or 45–51 g/m$^{2.7}$ in female patients – grade 1, 56–63 g/m$^{2.7}$ in male patients or 52–58 g/m$^{2.7}$ in female patients – grade 2, at least 64 g/m$^{2.7}$ in male patients or 59 g/m$^{2.7}$ in female patients – grade 3 [14].

Left atrium status was assessed by LAVI and reservoir strain indicators. Left atrial volume was calculated using a biplane disk summation approach for apical four- and two-chamber views. Left atrial dilatation was established with LAVI ≥ 34 mL/m^2. Two-dimensional speckle tracking echocardiography and subsequent speckle tracking analysis were performed on ultrasound images at a rate of at least 50 frames per second. Left atrial strain curves were constructed by manually tracking the endocardial border in the apical four-chamber view at end-diastole following the R – R algorithm (the R-wave is used as a zero reference point). Filling strain was defined as peak longitudinal LA strain [15].

DST was performed following with current Russian and international guidelines [8, 16]. Bicycle ergometry was used as exercise with a patient in sitting position and an initial load of 25 W for 3 minutes, followed by an 25 W increment every 3 minutes until the target heart rate (HR) of 85% of the maximum is achieved or symptoms (dyspnea) appear that do not allow the test to continue. Patients maintained a pedaling speed of 60 rpm throughout the test. During DST, 2D and Doppler echocardiograms were evaluated at rest and within not more than 2 minutes after exercise, the E/e' ratio and the peak tricuspid regurgitation velocity were analyzed. The criterion for a positive DST was increased E/e' ≥15 with a simultaneous increase in tricuspid regurgitation velocity ≥3.4 m/s.

MedCalc Statistical Software v.20.106 (https://www.medcalc.org; 2022) was used for the statistical analysis. The medians (Me) and the interquartile ranges [Q1; Q3] were determined for numerical variables and the sample rate for categorical variables. The statistical significance of the intergroup differences was assessed by the Mann-Whitney test and the chi-squared test.

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The predictive power of numerical variables was estimated by the areas under the error curves (ROC curves).

Results

The study included 98 patients from 40 to 82 years old, the majority of them were female (Table 1). The vast majority of patients (90.8%) were overweight or obese, every forth patient had diabetes mellitus, and every fifth patient had paroxysmal AF. All patients received combination antihypertensive therapy, which included angiotensin-converting enzyme inhibitors (or angiotensin II receptor blockers) and beta-blockers in 60.2% of cases. Most patients had achieved the target BP levels at the time of the examination. According to the echocardiographic findings, all patients had LVH accompanied by increased LV filling pressure and left atrial dilatation in 62 (63.3%) and 32 (32.7%) cases, respectively. LA reservoir strain ranged from 12.5% to 37.0% and was below the reference normal limit (36%) in 97 (99.0%) patients.

Patients were divided to two groups based on the DST results: Group 1 included 52 (53.1%) patients with negative DST and Group 2 included 46 (46,9%) patients with positive DST. In Group 2, the mean age of patients was higher, more patients had obesity, diabetes mellitus, and severe LVH. Mean LV filling pressure (E/e'), LAVI, and pulmonary artery pressure were higher and LA reservoir strain was lower in Group 2 than in Group 1 (Table 2).

The ROC-analysis showed that LA strain, LAVI, LV filling pressure (E/e'), and PASP can be used to predict DST results in patients with AH (Figure 1, Table 3).

LA strain has markedly higher predictive power compared to other echocardiographic indicators (Table 4). LA reservoir strain <22% allows predicting positive DST with the probability of 88.9% (76.5–95.2%). Higher values of LA strain suggest a negative DST with a probability of 88.7% (77.4–94.7%). The diagnostic accuracy of this criterion is 88.8% (81.0–93.6%).

Table 1. Characteristics of the examined patients with arterial hypertension

Parameter	Value
Age, years, Me [Q1; Q3]	60.5 [55.0; 66.0]
Male, n (%)	29 (29.6)
BMI, kg/m², Me [Q1; Q3]	30.5 [27.1; 33.4]
Overweight, n (%)	38 (38.8)
Obesity, n (%)	51 (52.0)
Diabetes mellitus, n (%)	25 (25.5)
Paroxysmal AF n (%)	18 (18.4)
ACE inhibitors/ARBs, n (%)	94 (95.9)
Beta blockers, n (%)	62 (63.3)
Thiazide diuretics, n (%)	44 (44.9)
Calcium channel blockers, n (%)	52 (53.1)
Target levels of BP, n (%)	78 (79.6)
LVH grade 1, n (%)	45 (45.9)
LVH grade 2, n (%)	35 (35.7)
LVH grade 3, n (%)	18 (18.4)
E/e', Me [Q1; Q3]	10.2 [8.6; 11.8]
E/e' > 9, n (%)	62 (63.3)
LAVI, mL/m2, Me [Q1; Q3]	31.0 [27.0; 35.0]
LAVI > 34 mL/m², n (%)	32 (32.7)
PASP, mm Hg, Me [Q1; Q3]	28.0 [26.0; 30.0]
PASP > 35 mm Hg, n (%)	2 (2.0)
LA reservoir strain, %, Me [Q1; Q3]	22.0 [19.0; 24.0]

ARB, angiotensin II receptor blocker; LVH, left ventricular hypertrophy; E/e', early transmitral filling velocity-to-mitral annular velocity ratio; ACE, angiotensin-converting enzyme; BMI, body mass index; LAVI, left atrial volume index; AF, atrial fibrillation; PASP, pulmonary artery systolic pressure.

Discussion

The study showed that DST detected HFpEF in almost 50% of patients with AH stage 2 complaining of dyspnea, palpitations, or non-anginal chest pain, which is fully consistent with the data on the wide prevalence of this disease and the essential role of AH in its development [17]. Most patients with AH and HFpEF shown by DST had moderate or severe LVH and obesity, many patients had diabetes mellitus and paroxysmal AF. They had higher mean values of E/e', LAVI, and PASP and lower LA reservoir strain than patients with AH and without HFpEF. Similar differences between patients with and without HFpEF were previously detected in several studies with invasive measurement of filling pressure at rest and during exercise [2, 5]. This is an indirect confirmation of high discriminatory power of DST in relation to HFpEF.

Our findings on the predictive power of various echocardiographic indicators also turned out to be comparable with the results of trials, in which HFpEF was verified using invasive measurement of filling pressure. For example, Reddy et al. [18] determined LA reservoir strain and E/e' in 363 patients with preserved LVEF, of whom, according to the invasive examination, 238 patients had HFpEF, and 125 patients had complaints of non-cardiac nature. LA reservoir strain had higher discriminatory power in relation to HFpEF than E/e': AUC 0.719 (95% CI 0.664–0.767) versus 0.601 (95% CI 0.563–0.639; p<0.0001). Again, according to our data, the area under the error curve was 0.922 (95% CI 0.851–0.967) for LA reservoir strain and 0.713 (95% CI 0.613–0.800; p=0.0002) for E/e'. Thus, both studies showed higher diagnostic power of LA reservoir strain as compared to the E/e' ratio, which has so far been considered the most informative non-invasive indicator of filling pressure.

Table 2. Characteristics of patients of the identified groups

Parameter	Patient groups		p
	Group 1 (n = 52)	Group 2 (n = 46)	
Age, years, Me [Q1; Q3]	56.0 [50.5; 61.5]	65.0 [60.0; 68.0]	< 0.0001
Male, n (%)	17 (32.7)	12 (26.1)	0.4769
Obesity, n (%)	19 (36.5)	32 (69.6)	0.0012
Diabetes mellitus, n (%)	5 (9.6)	20 (43.5)	0.0001
Paroxysmal AF n (%)	6 (11.5)	12 (26.1)	0.0648
LVH grade 2–3, n (%)	16 (30.8)	37 (80.4)	< 0.0001
E/e', Me [Q1; Q3]	9.0 [7.9; 11.1]	11.0 [9.4; 12.6]	0.0003
LAVI, mL/m2, Me [Q1; Q3]	28.0 [25.0; 32.9]	33.8 [29.0; 40.0]	0.0001
PASP, mm Hg, Me [Q1; Q3]	26.0 [25.0; 28.0]	29.0 [28.0; 30.0]	< 0.0001
LV strain, %, Me [Q1; Q3]	24.0 [22.0; 28.0]	19.0 [18.0; 21.0]	< 0.0001

LVH, left ventricular hypertrophy; E/e', early transmitral filling velocity-to-mitral annular velocity ratio; LAVI, left atrial volume index; LV, left ventricular; PASP, pulmonary artery systolic pressure.

Table 3. Characteristics of echocardiographic indicators as diagnostic criteria for heart failure with preserved ejection fraction

Parameter	AUC (95 % CI)	p	Criterion	Se (95 % CI)	Sp (95 % CI)
E/e'	0.713 (0.613–0.800)	< 0.0001	> 9.5	73.91 (58.9–85.7)	59.62 (45.1–73.0)
LAVI	0.724 (0.624–0.809)	< 0.0001	> 30	71.74 (56.5–84.0)	65.38 (50.9–78.0)
PASP	0.764 (0.668–0.844)	< 0.0001	> 28	67.39 (52.0–80.5)	76.92 (63.2–87.5)
LA strain	0.922 (0.851–0.967)	< 0.0001	≤ 21	86.96 (73.7–95.1)	90.38 (79.0–96.8)

AUC, area under the error curve; CI, confidence interval; Se, sensitivity; Sp, specificity; E/e', early transmitral filling velocity-to-mitral annular velocity ratio; LAVI, left atrial volume index; PASP, pulmonary artery systolic pressure.

Figure 1. ROC curves of left atrial (LA) strain, pulmonary artery systolic pressure (PASP), left atrial volume index (LAVI), and left ventricular filling pressure (E/e') as predictors of a positive diastolic stress test in patients with arterial hypertension

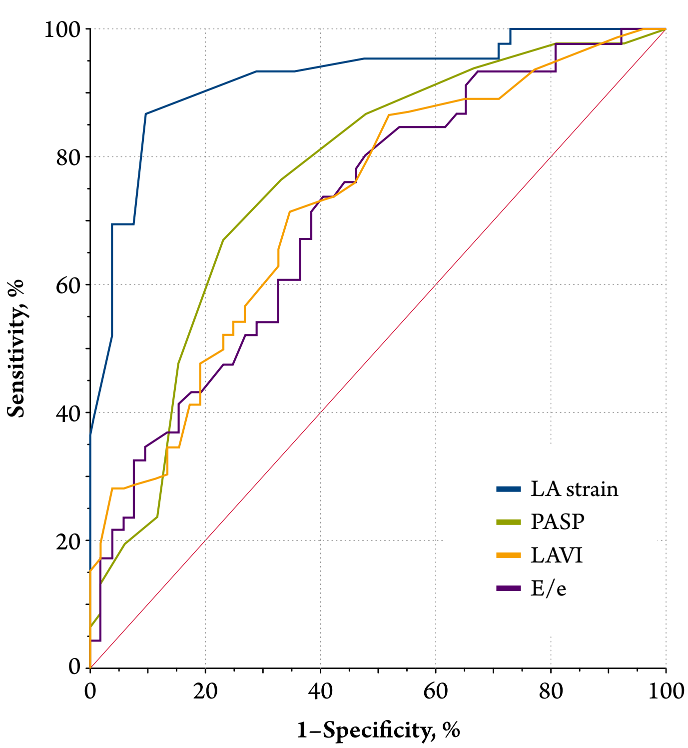

Table 4. Comparison of diagnostic capabilities of echocardiographic indicators for heart failure with preserved ejection fraction

Indicators compared		AUC difference	95% CI	p
LA strain	PASP	0.158	0.0478–0.268	0.0049
LA strain	LAVI	0.199	0.100–0.297	0.0001
LA strain	E/e'	0.209	0.0975–0.321	0.0002
PASP	LAVI	0.0406	–0.102–0.183	0.5765
PASP	E/e'	0.0514	–0.0858–0.189	0.4626
LAVI	E/e'	0.0109	–0.131–0.153	0.8805

AUC, area under the error curve; CI, confidence interval; E/e', early transmitral filling velocity-to-mitral annular velocity ratio; LAVI, left atrial volume index; LA, left atrial; PASP, pulmonary artery systolic pressure.

However, mean LA reservoir strain in patients with and without HFpEF were significantly lower in this study (19.6% versus 24.0%, respectively) than in the study by Reddy et al. (29±16% versus 40±13%, respectively). In our opinion, such pronounced differences can be explained by the characteristics of the included patients. Our study included patients with AH and LVH, i.e., with organic heart disease naturally causing LV diastolic dysfunction. Ye et al. [10] showed that reservoir strain decreases as LV diastolic dysfunction progressed from 40.2±4.6% in healthy

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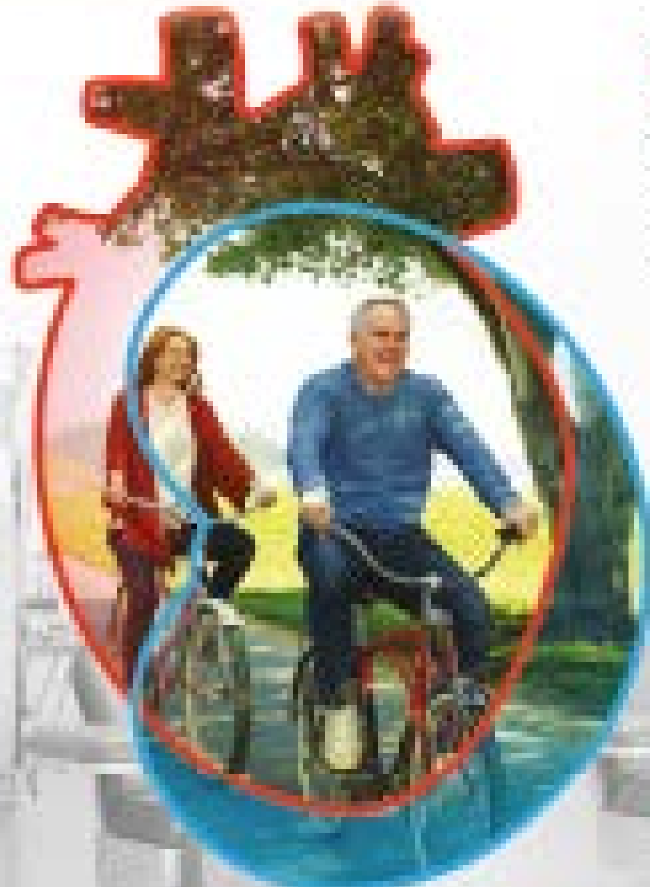
СОХРАНИТЬ САМУ ЖИЗНЬ

ФОРСИГА

NEW:

ХРОНИЧЕСКАЯ БОЛЕЗНЬ ПОЧЕК



ФОРСИГА – ЕДИНСТВЕННЫЙ ПРЕПАРАТ, ДОКАЗАВШИЙ ЗАМЕДЛЕНИЕ ПРОГРЕССИРОВАНИЯ ХБП НА 39%

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individuals to 36.0±4.7% in diastolic dysfunction stage 1, 29.6±4.8% in stage 2, and 22.4±6.0% in stage 3. Mean strain values correspond to diastolic dysfunction stage 3 in patients with HFpEF included in this study and stage 2 in patients without HFpEF, and in the study by Reddy et al., the group of subjects with HFpEF consisted of patients with diastolic dysfunction stage 2 and the group of subjects without HFpEF was represented by individuals without organic heart disease.

The study by Lin et al. [11] included patients with stable coronary artery disease (CAD) suggesting the presence of more or less severe LV diastolic dysfunction, i.e., comparable in this respect with the patients included in this study. Mean LA reservoir strain in patients with and without HFpEF was 25.6 ± 5.4% and 20.9±3.7%, respectively, i.e., the values were virtually the same as the results of this study.

Lin et al. [11] assessed LA myocardial stiffness by the ratio of reservoir strain to E/e'sept. They examined 60 patients with stable CAD, and invasively measured LV end-diastolic pressure (EDP) at rest was ≤15 mm Hg in 27 patients and >15 mm Hg in 33 patients. In Group 2, LA reservoir strain was lower (20.9±3.7 versus 25.6±5.4, respectively; p<0.01), but E/e'sept was higher (13.1±2.9 versus 11.3±2,9, respectively; p=0.02) and the ratio of reservoir strain to E/e'sept was also higher (1.7±0.5 versus 2.4±0.6, respectively; p<0.01). ROC analysis showed that the predictive power of the ratio of reservoir strain to E/e'sept in relation to increased LVEDP (AUC=0.83; 95% CI 0.71–0.92) is higher than that of reservoir strain (AUC = 0.75; 95% CI 0.62–0.85) and E/e'sept (AUC=0.76; 95% CI 0.63–0.86). Sensitivity and specificity of the reservoir strain/E/e'sept ratio >2.1 are 87.9% and 74.1%, respectively, of reservoir strain <24.7% – 87.9% and 59.3%, respectively, and E/e'sept > 11.1–84.9% and 66.7%, respectively. Thus, myocardial stiffness had the highest predictive power to detect elevated LVEDP during invasive examination in patients with CAD and preserved LVEF.

Despite the difference in mean strain, the cut-off values for patients with HFpEF were almost the same in the studies mentioned above: 24.5% according to Reddy et al. and 24.7% according to Lin et al. In this study, the cut-off value was lower (21%), which is the same as the findings by Lundberg et al. [19] and very close to the data obtained by Mandoli et al. (20%) [20]. Noteworthy, both lower and higher cut-off values are found in the literature. For example, Aung et al. [21] suggest that LA reservoir strain < 17.5% as the criterion for HFpEF, Inoue et al. [22] and Singh et al. [23] suggest 18%, and Telles et al. [24] – 33%. The variability of values can be associated with different ratios of patients who have increased filling pressure at rest and during exercise, since the predominance of patients with initially high filling pressure (and low reservoir strain) moves the cut-off values towards lower values and vice versa.

Thus, the results of this study are fully consistent with the results of previous studies, supporting the possibility of using LA reservoir strain for the diagnosis of HFpEF. This study specifically demonstrated that the assessment of LA reservoir strain can be used in the non-invasive diagnosis of HFpEF instead of DST. The diagnoses made based on the strain values and the results of DST match in about 90% of cases. It appears reasonable to conduct research in this area, ideally using invasive diagnosis of HFpEF.

Conclusion

Left atrial reservoir strain can be used for non-invasive diagnosis of heart failure with preserved ejection fraction to predict the result of the diastolic stress test in patients with arterial hypertension and left ventricular hypertrophy if it cannot be performed. A decrease in reservoir strain to 21% or less allows predicting positive diastolic stress test with a probability of 88.9% (76.5–95.2%). Higher values of LA strain suggest a negative diastolic stress test with a probability of 88.7% (77.4–94.7%). The diagnostic accuracy of this criterion is 88.8% (81.0–93.6%).

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