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An Increase in the Left Atrium Volume During Exercise is Associated With a Positive Result of a Diastolic Stress Test in Patients With Arterial Hypertension

Aim To study the relationship between changes in left atrial volume (LAV) during exercise and the result of a diastolic stress test (DST) in patients with arterial hypertension (AH).

Material and methods The study included 219 patients with AH without ischemic heart disease and atrial fibrillation. During the DST performed before and after exercise, the ratio of transmitral flow velocity to mitral annular velocity (E/e'), the left atrial global longitudinal strain in the reservoir phase (reservoir strain), and LAV were determined. The criterion for a positive DST was an increase in E/e' ≥15.

Results A positive result of DST was observed in 90 (41.1%) patients. Patients with positive DST were older (65.0 and 59.0 years); among them, there were fewer men (24.4 and 41.1%), but more patients with obesity (66.7 and 40.3%) and diabetes mellitus (36.7 and 8.5%). At rest, patients with positive DST had higher E/e' ratio (11.5 and 8.8), pulmonary artery systolic pressure (29.0 and 27.0 mm Hg), and LAV (60.0 and 52.0 ml), but a lower left atrial reservoir strain (20.0 and 24.0%). During exercise in patients with positive and negative DST, E/e' increased by 5.46 and 0.47 units, respectively. Changes in the LAV and reservoir strain during exercise in these groups were directed differently. In patients with positive DST, the left atrial reservoir strain decreased by 1.0 percentage points (pp) whereas in patients with negative DST, it increased by 8.0 pp. During exercise, the LAV increased by 10.0 ml in patients with a positive DST, whereas in the alternative group, the LAV decreased by 8.5 ml. The AUC for changes in LAV as an indicator of a positive DST was 0.987 while the AUC for the resting left atrial reservoir strain was 0.938. An increase in LAV >1 ml, as an indicator of a positive DST has a sensitivity of 96.9% and a specificity of 95.1%.

Conclusion In AH patients, changes in left ventricular filling pressure are associated with a unidirectional change in LAV. An increase in LAV during exercise by more than 1 ml can serve as a criterion for a positive DST result. This assessment was consistent with the assessment of the DST result by the E/e' criterion >15 in 94.5% of cases.

Keywords Heart failure with preserved ejection fraction; arterial hypertension; diastolic stress test; atrial cardiomyopathy; speckle tracking technology; left atrial myocardial strain; left atrial volume

For citations Mazur E. S., Mazur V. V., Bazhenov N. D., Nilova O. V., Nikolaeva T. O., Alekseev D. V. An Increase in the Left Atrium Volume During Exercise is Associated With a Positive Result of a Diastolic Stress Test in Patients With Arterial Hypertension. Kardiologiia. 2024;64(3):11–17. [Russian: Мазур Е.С., Мазур В.В., Баженов Н.Д., Нилова О.В., Николаева Т.О., Алексеев Д.В. Увеличение объема левого предсердия при физической нагрузке ассоциируется с положительным результатом диастолического стресс-теста у больных артериальной гипертензией. Кардиология. 2024;64(3):11–17].

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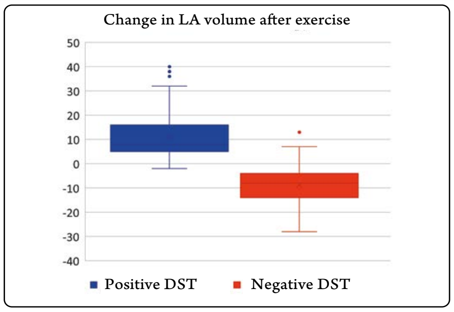
Introduction

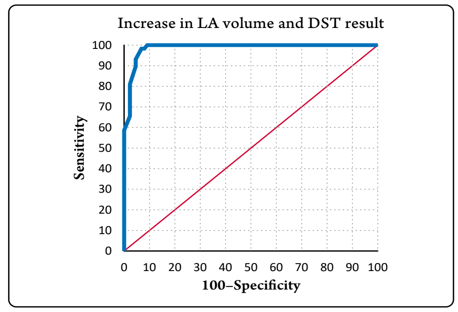
Invasive measurement of left ventricular filling pressure is the gold standard for diagnosing heart failure with preserved ejection fraction (HFpEF). However, due to the high prevalence and clinical relevance of this pathology, there is an urgent need to develop diagnostic methods suitable for widespread clinical use [1]. One such method is the diastolic stress test (DST), an exercise stress test under echocardiographic control in which the response of left ventricular filling pressure to exercise is assessed by the change in the E/e' ratio, i.e., the ratio of early transmitral filling velocity (E) to mitral annular velocity (e'). An increase in E/e' during exercise to 15 or more is the criterion for a positive DST. Pulmonary artery systolic pressure (PASP) of 50 mm Hg or higher is an additional criterion [2,3]. DST can be used instead of invasive filling pressure measurement [4] when existing algorithms for determining the probability of HFrEF cannot reject or accept this diagnosis due to its extremely low or extremely high probability [5, 6].

DST is much more widely available than invasive pressure measurement, but it has its drawbacks. First, it should be noted that DST results are highly dependent on the accuracy of measurements of transmitral velocity,

Central illustration. An Increase in the Left Atrium Volume During Exercise is Associated With a Positive Result of a Diastolic Stress Test in Patients With Arterial Hypertension

Diastolic stress test (DST) was performed in 219 patients with hypertension (54.2% were male patients, mean age 60.5 ± 8.7 years). Left atrial (LA) volume increased after exercise in 88 (97.8 %) of 90 DST-positive patients and decreased in 118 (91.5 %) of 129 DST-negative patients





In patients with hypertension, an increase in LA volume of more than 1 ml during exercise can serve as a criterion for a positive DST result (sensitivity 96.9 %, specificity 95.1 %).

LA, left atrium; DST, diastolic stress test.

mitral annular velocity, and tricuspid regurgitation velocity during exercise, i.e., at high heart rate and deep, rapid breathing. Under these conditions, E/e' is not measurable in 20% of cases and tricuspid regurgitation velocity is not measurable in 50% of cases, making it relevant to search for alternative methods to assess the response of left ventricular filling pressure to exercise [7].

It is known that in the absence of atrial fibrillation and mitral valve disease, left atrial (LA) volume depends on left ventricular filling pressure [8], allowing European experts to consider left atrial dilatation as an important criterion for the diagnosis of HFrEF [6]. However, based on the literature, the relationship between exercise-induced changes in LA volume and DST findings has not been previously investigated.

Objective

Investigate the relationship between changes in LA volume during exercise and DST findings in patients with hypertension.

Material and methods

The single-center, cross-sectional study was approved by the Ethics Committee of the Tver State Medical University (Minutes No. 7 dated 23.04.2020) and was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki. All included patients signed a voluntary informed consent for the use of their research results for scientific purposes.

The study included patients with previously diagnosed hypertension who underwent transthoracic echocardiography (TTE), stress echocardiography, and 24-hour electrocardiogram (ECG) monitoring to determine the cause of complaints of dyspnea or chest pain. Continuous use of at least two antihypertensive agents was considered a criterion for previously diagnosed hypertension. Patients without left ventricular hypertrophy, with left ventricular ejection fraction less than 50%, with previously diagnosed coronary artery disease or signs of transient myocardial ischemia detected by stress echocardiography, and patients with previously diagnosed atrial fibrillation or atrial fibrillation detected by 24-hour ECG monitoring were excluded from the study.

Sex and age of the patients, the presence of concomitant diabetes mellitus and obesity, administration of antihypertensive drugs and blood pressure (BP) at the time of the study were taken into consideration. Obesity was diagnosed with a body mass index of 30.0 kg/m^2 or greater. The target BP level was less than 140/90 mm Hg.

DST was implemented in accordance with current Russian and international guidelines [2, 3, 7]. Exercise was performed by bicycle ergometry with the patient in a seated position and an initial load of 25 W for 3 minutes, followed by an increase of 25 W every 3 minutes until the target HR of 85% of maximum was reached or symptoms (dyspnea) occurred that made it impossible to continue the test. Patients maintained a cadence of 60 rpm throughout the test.

Echocardiography was performed with a Vivid S70 ultrasound scanner (GE, USA) before and within 2 minutes after the end of the exercise test; peak transmitral velocities in the early (E) and atrial (A) filling phases, mitral annular velocity (e'), and tricuspid regurgitation velocity were measured. The E/e' ratio and the pulmonary artery systolic pressure (PASP) were calculated. The criterion for a positive DST was an increase in E/e'

ISSN 0022-9040. Kardiologiia. 2024;64(3). DOI: 10.18087/cardio.2024.3.n2643

≥15, independent of PASP. Minimal, presystolic, and maximal LA volumes were calculated using a biplane disk summation approach for the apical four- and two-chamber views. Visualization of the examined structures and calculation of ultrasound parameters were performed according to the current ASE and EACVI guidelines [9].

Two-dimensional speckle-tracking echocardiography and subsequent 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 using the R-R algorithm (the R wave is used as the zero-reference point). Filling strain was defined as peak longitudinal LA strain [10].

Statistical analysis was performed using MedCalc® Statistical Software version 22.006 (MedCalc Software Ltd, Belgium). The values of categorical variables are presented as absolute and relative numbers of carriers of a trait – n (%); the chi-squared test was used to assess differences between groups, and two-tailed Fisher's exact test in the presence of cells with less than 5 observations in the four-fold table. Because the distribution of most numeric variables was non-normal, medians with interquartile ranges (Me [Q1; Q3]) were used to express their mean values when describing the contingent of patients studied, and medians with 95% confidence intervals (Me (95% CI)) were used when comparing selected groups. The Mann-Whitney test was used to assess statistical significance of differences between groups, and the Wilcoxon test was used to assess statistical significance of changes in numerical variables. ROC analysis was used to assess the predictive power of the variables, and the area under the error curve (AUC) was compared according to DeLong et al. Correlation analysis was used to examine the relationship between the numerical variables. Statistical analysis results were considered significant when the null hypothesis probability was less than 5% (p<0.05).

Results

Of the 219 patients included in the study, 75 (34.2%) were male, median age was 61.0 [55.0; 67.0] years, and history of hypertension was 7.0 [5.0; 10.0] years; 112 (51.1%) of the subjects were obese and 44 (20.1%) had diabetes mellitus. All patients received combined antihypertensive therapy, including angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers in 213 (97.3%) cases, beta-blockers in 121 (55.3%) cases, diuretics in 111 (50.7%) cases, and calcium channel blockers in 108 (49.3%) cases. BP was less than 140/90 mm Hg in 113 (51.6%) of the patients at the time of the examination. Median left ventricular mass index (LVMI) was 127.0 [118.0; 137.8] g/m² in male patients and 112.0 [104.0; 123.0] g/m² in female patients. Median left atrial volume index (LAVI) was 28.0 [25.0; 34.0] mL/m².

DST was positive in 90 (41.1%) of the 219 patients examined. As shown in Table 1, patients with a positive DST were on average older, had a longer history of hypertension, were less likely to be male, but more likely to be obese and to have diabetes mellitus. Patients with a positive DST were more likely to receive beta-blockers, but there was virtually no difference in the efficacy of antihypertensive therapy in the compared groups.

At rest, DST-positive patients had higher mean values of LVMI, LA volume, LAVI, and PASP, but lower mean values of reservoir strain (Table 2). Transmitral velocity in the early (E) and atrial (A) filling phases did not differ between the selected groups, but mitral annular velocity (e') was lower in DST-positive patients than in the alternative group. As a result, the E/e' ratio, which reflects left ventricular filling pressure, was significantly higher in patients with positive DST.

During exercise, both mitral annular velocity (e') and early diastolic transmitral velocity (E) increased in DST-negative patients, leaving the E/e' ratio almost unchanged. Accelerated early transmitral flow was also associated with decreased presystolic LA volume. This was accompanied by an increase in transmitral velocity during the atrial filling phase (A), resulting in a decrease in minimum LA volume and an increase in reservoir strain.

Table 1. Clinical characteristics of hypertensive patients with negative and positive diastolic stress test results

Parameter	Diastolic stress test result		
	Negative (n=129)	Positive (n=90)	p
Age, years	59.0 (56.9–60.1)	65.0 (63.0–67.0)	< 0.0001
Male, n (%)	53 (41.1)	22 (24.4)	0.0109
Obesity, n (%)	52 (40.3)	60 (66.7)	0.0001
Diabetes mellitus, n (%)	11 (8.5)	33 (36.7)	< 0.0001
History of hypertension, years	6.0 (5.0–7.0)	9.0 (8.0–10.0)	< 0.0001
ACE inhibitors/ARBs, n (%)	126 (97.7)	87 (96.7)	0.6538
Calcium channel blockers, n (%)	66 (51.2)	42 (46.7)	0.5136
Diuretics, n (%)	61 (47.3)	50 (55.6)	0.2296
Beta-blockers, n (%)	61 (47.3)	60 (66.7)	0.0046
BP <140/90 mm Hg, n (%)	69 (53.5)	44 (48.9)	0.5038

Numerical values are presented as the medians and 95 % confidence intervals (Me (95 % CI)). Categorical variables are expressed as absolute and relative numbers of carriers of a trait (n (%)). BP, blood pressure; ARB, angiotensin II receptor blocker; ACE, angiotensin-converting enzyme.

In patients with a positive DST, the rate of left ventricular relaxation during exercise remained virtually unchanged, and early diastolic transmitral velocity increased markedly, resulting in an increased E/e' ratio that allowed us to declare a positive DST. Transmitral velocity in the atrial filling phase (A) also increased during exercise, but to a much lesser extent than in the alternative group. As a result of insufficient transmitral blood flow acceleration during atrial systole, the minimum LA volume increased, and the reservoir strain decreased.

Thus, patients with a positive and negative DST differed both in the structural and functional state of the left heart at rest and in their response to exercise. To explore the possibility of using these differences to predict a positive DST, all patients studied were randomized 2:1 into a derivation cohort and a validation cohort. In the derivation cohort, the reservoir strain at rest and the increase in LA volume during exercise were most closely associated with DST results (Figure 1). Area under the error curve (AUC) was 0.938 (95% CI 0.886–0.971) for the reservoir strain and 0.987 (0.952–0.998) for the increase in LA volume.

Area under the error curve was significantly smaller for the indices reflecting the structural and functional state of the left ventricle before exercise. AUC was 0.735 (0.656–0.805) for mitral annular velocity (e') and 0.605 (0.521–0.685) for LVMI.

The cut-off points for the increase in LA volume and the reservoir strain were 1 mL and 21%, respectively. In the validation cohort, the AUC for «increase in LA volume >1 mL» as a predictor of a positive DST was 0.960 (0.886–0.992), the sensitivity was 96.9 (83.8–99.9) %, the specificity was 95.1 (83.5–99.4) %, and the likelihood ratios for positive and negative results were 19.86 and 0.033, respectively. The coefficient of agreement (Cohen's kappa) with the DST results was 0.917 (0.825–1.000). For the «reservoir strain≤21%» criterion, the AUC was 0.883 (0.787–0.947), the sensitivity was 93.8 (79.2–99.2) %, the specificity was 82.9 (67.9–92.8) %, and the likelihood ratios for positive and negative results were 5.49 and 0.075, respectively. Cohen's kappa was 0,754 (0,605–0,903).

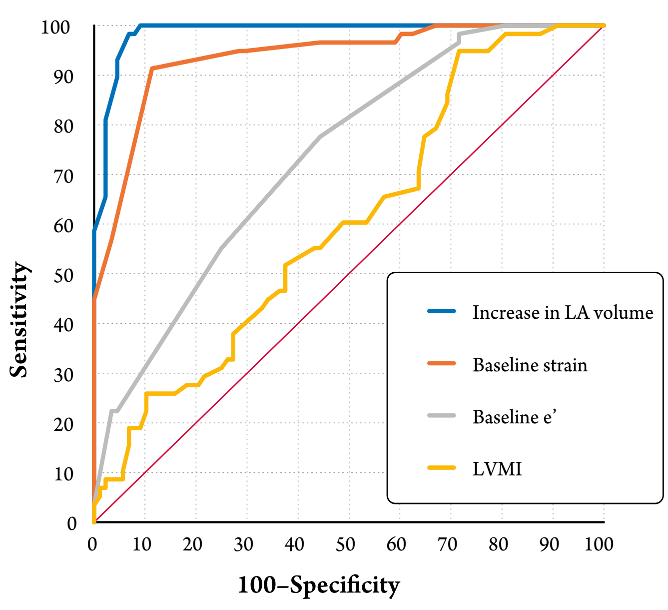
The increase in LA volume can be used to predict DST results because there is a correlation between the change in E/e' ratio during exercise and the change in LA volume (Figure 2). The coefficient of correlation between these two indicators was 0.6047 (95% CI: 0.5133–0.6826), p<0,0001. Therefore, based on the results of this study, the change in LA volume during exercise is associated with the change in left ventricular filling pressure.

Table 2. Left ventricular status in hypertensive patients before diastolic stress test

Parameter	Diastolic stress test result: Negative (n=129)	Positive (n=90)	p
LVMI, male patients, g/m2	122.0 (118.0–131.0)	137.0 (126.0–139.20)	0.0033
LVMI, female patients, g/m²	107.5 (104.0–111.0)	115.5 (112.0–120.0)	< 0.0001
Minimum LA volume, mL	18.0 (16.0–20.0)	23.0 (21.0–28.8)	< 0.0001
Presystolic LA volume, mL	34.0 (31.0–37.0)	40.0 (39.2–43.8)	< 0.0001
Maximum LA volume, mL	52.0 (48.0–55.1)	60.0 (56.2–64.0)	0.0001
LAVI, mL/m²	27.0 (26.0–28.1)	30.0 (29.0–33.4)	0.0001
PASP, mm Hg	27.0 (27.0–27.0)	29.0 (28.0–30.0)	< 0.0001
E, cm/s	63.0 (59.9–65.0)	60.0 (56.2–63.0)	0.2473
A, cm/s	74.0 (70.0–76.1)	74.0 (71.0–77.0)	0.9154
e', cm/s	7.0 (7.0–7.0)	5.0 (5.0–6.0)	< 0.0001
E/e'	8.8 (8.7–9.4)	11.5 (11.0–11.8)	< 0.0001
Reservoir strain, %	24.0 (23.0–25.0)	20.0 (19.0–21.0)	< 0.0001

Numerical values are presented as the medians and 95 % confidence intervals (Me (95 % CI)). LVMI, left ventricular mass index; LA, left atrium; LAVI, left atrial volume index; PASP, pulmonary artery systolic pressure; e', mitral annular velocity; E, early diastolic transmitral velocity; A, transmitral velocity in atrial systole.

Figure 1. Error curves for left atrial (LA) volume increase during exercise, left atrial strain during the reservoir phase, and pre-exercise mitral annular velocity (e') and left ventricular mass index (LVMI) as predictors of a positive diastolic stress test result



ISSN 0022-9040. Kardiologiia. 2024;64(3). DOI: 10.18087/cardio.2024.3.n2643

Discussion

According to Obokata et al [4], who compared the results of DST with the results of invasive diagnosis of HFrEF, the sensitivity of DST is 90 (79–96) %, the specificity is 71 (51–85) %, and the likelihood ratios for positive and negative results are 3.1 and 0.1, respectively. The relatively poor discriminative ability of DCT is largely related to the errors in Doppler measurement of transmitral velocities and mitral annular velocity at sharply elevated heart rate during exercise, making it relevant to search for new non-Doppler criteria of positive DCT results [7]. According to this study, an increase in LA volume of 1 mL or more during exercise may be such a criterion. Assessment of DST results by traditional criteria and changes in LA volume agree in 95.9% of cases (coefficient of agreement 0.917).

It should be noted that LA volume measurement before and after exercise can be performed during a conventional ischemic stress test, which allows this examination not only to detect (exclude) transient myocardial ischemia, but also to assess the likelihood that the patient has HFrEF.

This study confirmed the feasibility of using reservoir strain at rest to predict DST results [11, 12]. According to Ye et al. [11], the area under the error curve for reservoir strain as a predictor of positive DST is 0.79 (0.74–0.83), while according to our data it is 0.883 (0.787–0.947). With a reservoir strain of 21% or less, the probability of a positive DST result is 83.0%, making it feasible to perform the DST. Higher reservoir strain values indicate a high probability of a negative test result (94.1%), which allows the stress test to be abandoned. Therefore, determining left atrial strain in the reservoir phase using echocardiography seems to be quite reasonable in patients with complaints that are characteristic of heart failure and with a preserved left ventricular ejection fraction.

The results of this study somewhat extend the existing understanding of the mechanism of HFrEF. According to current guidelines, the main pathogenetic mechanism of HFrEF is impaired left ventricular relaxation. The role of left atrial dysfunction in the development of HFrEF is not considered, although it is recognized that atrial fibrillation may lead to its decompensation [8, 13]. Meanwhile, according to this study, the result of DST depends not so much on the left ventricle as on the left atrium's initial state and response to exercise. This is evidenced by the fact that reservoir strain, which reflects left atrial status, is more closely related to DST results than LVMI and mitral annular velocity, which reflects left ventricular relaxation capacity.

The results of numerous studies suggest that a decrease in left atrial strain during the reservoir phase is associated with the development of atrial fibrosis [14], which serves as a morphologic substrate for type II atrial cardiomyopathy [15]. Atrial cardiomyopathy is a set of structural, functional, and electrophysiological changes in the atrial myocardium that result in the manifestation of clinical symptoms [15]. In DST-positive patients, an increase in LAVI can be considered

Figure 2. Scatter plot showing the relationship between the change in left ventricular filling pressure (E/e') and the change in left atrial (LA) volume during exercise

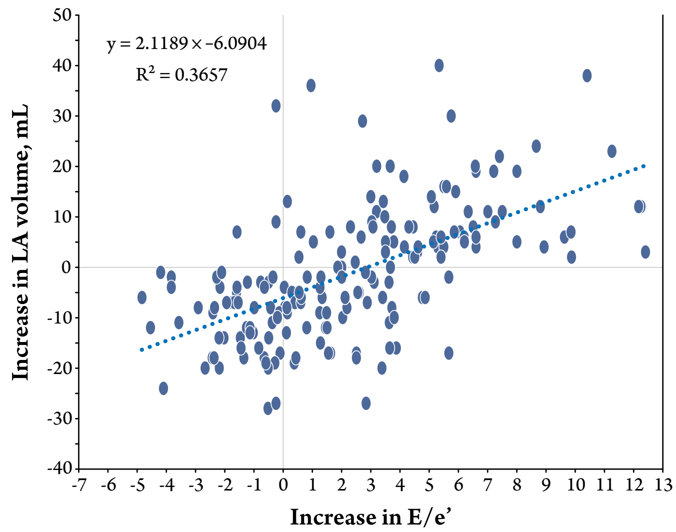


Table 3. Changes in left heart condition in hypertensive patients with negative and positive results of diastolic stress test during exercise

Change during exercise	Diastolic stress test result: Negative (n=129)	Diastolic stress test result: Positive (n=90)	p
Minimum LA volume, mL	-5.0 (-6.0–-4.5)	7.5 (6.5–8.5)	< 0.0001
Presystolic LA volume, mL	-7.0 (-8.0–-5.5)	9.0 (7.5–10.0)	< 0.0001
Maximum LA volume, mL	-8.5 (-10.0–-7.0)	10.0 (8.0–12.0)	< 0.0001
e', cm/s	1.5 (1.5–2.0)	0.0 (0.0–0.5)	< 0.0001
E, cm/s	19.0 (16.5–22.0)	34.5 (31.0–37.5)	< 0.0001
E/e'	0.47 (0.02–0.90)	5.46 (4.90–6.05)	< 0.0001
PASP, mm Hg	10.5 (10.0–11.0)	19.0 (18.5–20.0)	< 0.0001
Reservoir strain, %	8.0 (6.8–9.5)	-1.0 (-1.5–-0.5)	< 0.0001
A, cm/s	17.5 (15.5–20.0)	6.0 (4.0–8.5)	< 0.0001

The difference between the exercise and rest medians and the 95 % confidence interval of this difference are shown. LA, left atrium; PASP, pulmonary artery systolic pressure; e', mitral annular velocity; E, early diastolic transmitral velocity; A, transmitral velocity in atrial systole.

a structural manifestation of atrial cardiomyopathy and a decrease in reservoir strain can be considered a functional manifestation. Atrial fibrillation is a typical clinical manifestation of electrophysiological abnormalities in atrial cardiomyopathy, but such patients were excluded from this study.

Aging, hypertension, obesity, and diabetes mellitus contribute significantly to the development of atrial cardiomyopathy [15]. The same factors are considered to be inducers of systemic inflammation, resulting in endothelial dysfunction of the coronary microcirculation and impaired relaxation of the left ventricular myocardium [13]. In fact, DST-positive patients were older, more likely to have obesity and diabetes mellitus, on the one hand, and had significantly lower reservoir strain and mitral annular velocity, on the other hand.

Thus, the results of this study allow us to consider that the result of DST depends not only on the state of the left ventricle, but also on the state of the left atrium, in particular on its ability to increase its contractile activity during exercise.

Limitations

The study was conducted in a highly selective group of patients and its results cannot be extrapolated to the entire population of patients with potential HFrEF, particularly those with coronary artery disease and atrial fibrillation. Furthermore, the high discriminative power of LA volume changes with respect to DST does not mean that this criterion is equally effective with respect to HFrEF detected by invasive examination. It is clear that these two issues require special research.

Conclusion

Changes in left ventricular filling pressure are associated with unidirectional changes in LA volume in patients with hypertension. An increase in LA volume of more than 1 mL during exercise may be a criterion for a positive DST result. This assessment is consistent in 94.5% of cases with the assessment of the DST result according to the E/e' >15 criterion.

No conflict of interest is reported.

The article was received on 21/01/2024

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