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Some indicators of left ventricular dysfunction in hypertensive patients, depending on the level of matrix metalloproteinases and tissue inhibitors of metalloproteinase-1

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Abstract

Aim. To study the level of matrix metalloproteinases-1 and -2, and tissue inhibitor of metalloproteinases-1, the indicator of left ventricular myocardial deformation in patients with stage 1–2 hypertension.

Methods. 114 patients (40 women and 74 men) with hypertension of 1–2 stages observed in the cardiology "Department of the Road clinical hospital Chita II" were examined. The median age was 42±8.3 years. Left ventriclular diastolic function was studied by using tissue Doppler imaging in apical four-chamber views. Serum matrix metalloproteinase-1, matrix metalloproteinase-2, and tissue inhibitor of metalloproteinases-1 levels were measured in all patients on automated immunoassay analyzers using ready-to-use ELISA kits.

Results. An increase in serum levels of matrix metalloproteinases-1 and -2 in the group of patients with hypertension and diastolic dysfunction by 46 and 47%, respectively, was found against increased levels of serum tissue inhibitor of metalloproteinase-1 ($p=0.049$). In patients with diastole dysfunction, myocardial global longitudinal strain was decreased in was observed by 22.8% compared with patients without diastole dysfunction ($p <0.05$). The analysis revealed a moderate negative relationship between left ventricular global longitudinal strain and the serum levels of metalloproteinases-2 ($r=0.64$, $p <0.05$).

Conclusion. In patients with hypertension and left ventricular diastolic dysfunction, a decrease in left ventricular global longitudinal strain is associated with the serum level of matrix metalloproteinase-2; a tissue inhibitor of metalloproteinases-1 is unrelated to left ventricular global myocardial strain.

Keywords: arterial hypertension, diastolic dysfunction, matrix metalloproteinases, MMPs, myocardial hypertrophy.

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Background. The results of the EPOCH study that was performed in 2003–2005 in four regions of the European part of the Russian Federation revealed that only 9% of patients had a reduced ejection fraction of <40%, the main cohort (ejection fraction of 20%–40%) accounted for 20% of patients with chronic heart failure, and the contractile function was not generally affected in 71% of patients [1]. The processes of increased collagen accumulation in the extracellular matrix and diastolic dysfunction (DD), along with impaired nitroxide-producing endothelial function, imbalanced atrial peptide system, and impaired renin-angiotensin-aldosterone system, are the mechanisms of heart failure in patients with the hypertensive disease (HD) [2].

The main pathway that implements the profibrogenic effect in this category of patients is the effect of angiotensin II on the metalloproteinase-1 (MMP1) system and its tissue inhibitor [1]. Matrix metalloproteinases (MMPs) are endopeptidases that are directly involved in collagen cleavage. Thus, activated MMPs are completely blocked by MMP tissue inhibitors [3].

The level of MMP1 tissue inhibitor in the blood is known to affect the development of chronic heart failure, being a predictor of impaired diastolic filling of the left ventricle (LV) of the heart. Therefore, some authors consider this indicator as a potential marker of non-invasive diagnostics of fibrosis [4–6].

In the light of modern advances in the study of heart failure [5–7], we assume the relationship between the impaired MMP system and LV strain, as well as their influence on the progression of dia-

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stolic heart failure in patients with HD. However, the literature revealed no data on the listed mechanisms that contribute to systolic dysfunction in this category of patients with impaired myocardial relaxation without hypertrophy.

The study aimed to analyze the level of MMP1 and MMP2, as well as the MMP1 tissue inhibitor concerning the index of global LV myocardial strain in patients with stage 1–2 HD, depending on the presence of LV DD.

Materials and methods. The study involved 114 patients (40 females and 74 males) with stage 1–2 HD, who were monitored in the cardiology department of the Road Clinical Hospital, St. Chita II, from 2017 to 2020. Patients did not receive antihypertensive therapy, as they were referred from a medical examination and their diagnosis was established for the first time. All patients were examined before the prescription of antihypertensive therapy.

The studied patients with HD were distributed into two groups depending on the presence of DD, thus group 1 included patients with HD having normal diastole (43 patients, 58%), and group 2 included patients with HD having impaired DD (31 patients, 42%).

In the group of patients with HD without DD, the average age was 42 ± 8.3 years, wherein females were older than males (44.84 ± 1.13 and 40.03 ± 1.15 years, respectively, $p = 0.67$). The disease duration in group 1 averaged 9.2 ± 0.6 years (8.33 ± 0.75 years for males, 10.55 ± 0.97 years for females, $p = 0.51$).

In patients with HD having DD, the average age was 42 ± 4.9 years, and females were older than males (44.7 ± 4.3 and 43.5 ± 3.2 years, respectively, $p = 0.74$). The disease duration in group 2 averaged 10.3 ± 2.1 years (10.4 ± 0.8 years for males and 9.1 ± 1.1 years for females, $p = 0.59$).

A family history of cardiovascular diseases (HD, myocardial infarction, and acute cerebrovascular accident in first-degree relatives) was noted in 102 (92.9%) patients.

The control group included 35 healthy people according to the medical examination, without bad habits and signs of cardiovascular and other chronic diseases, who voluntarily agreed to participate in the study. The average age was 40.1 ± 1.49 years for males (23 people) and 42.8 ± 4.3 years for females (12 people), which was comparable to groups 1 and 2 ($p = 0.62$ and $p = 0.74$, respectively).

The diagnosis was verified based on the analysis of clinical data, as well as clinical and instrumental studies, including 24-hour blood pressure monitoring and electrocardiography according to generally accepted methods.

The inclusion criterion in the study was HD stage 1–2, grade 1–2, with a risk of 2–3. Exclusion criteria were ischemic heart disease, diabetes mellitus, and symptomatic arterial hypertension.

The study included patients with HD having an LV myocardial mass index (LVMM) of up to 110 g/m^2 and a relative LV wall thickness of up to 0.45 in patients without DD (group 1) and with DD (group 2) to identify the earliest changes in the global longitudinal LV strain.

The study was approved by the local ethics committee on January 31, 2017, protocol No. 83.

Doppler echocardiography was performed following the standard technique with the patient on the left side on a VIVIDE 95 apparatus with a multifrequency (1.5–4.6 MHz) matrix transducer M5S in the second harmonic mode. The interventricular septum and posterior wall thickness were determined, LVMM was calculated using the Cube equation, the LVMM index was determined as the ratio of LVMM to the body surface area, and the relative thickness of the LV walls was calculated.

The volumetric indices of the LV and atrium were obtained in the B-mode by tracing the boundaries of the endocardium in apical 4- and 2-chamber positions in systole and diastole (disc method), the left atrial volume index was calculated as the ratio of the left atrial volume to the body surface area. LV DD was investigated using a pulsed-wave Doppler imaging of tissues from the apical approach at the level of four chambers. The Doppler spectrum was recorded from the medial and lateral parts of the annulus fibrosus of the mitral valve, the velocity Em, and the E/Em ratio were assessed. The angle between the direction of the ray and the longitudinal motion of the structures was tried to be minimized to obtain the maximum values of the velocities during the Doppler imaging of the tissues.

LV diastolic function was assessed in all patients following the recommendations of the American Society of Echocardiography/European Association for Cardiovascular Imaging (2016) [8]. Following these recommendations, the presence of LV DD was determined by the criteria of the E/Em ratio of >14, the velocity of the medial part of the annulus fibrosis of the mitral valve Em was <7 cm/s that of the lateral part Em was <10 cm/s, the left atrial volume index was >34 ml/m^2, and the maximum tricuspid regurgitation velocity was >2.8 m/s. The detection of 3 or more criteria was regarded as the presence of LV DD. Normal LV diastole was established in the presence of 1 sign, and the detection of 2 of the listed criteria was regarded as an indeterminate result.

MMP1, MMP2, and tissue inhibitor MMP1 in the blood serum were quantified in all subjects at

Table 1. Level of metalloproteinases and their tissue inhibitor.

Parameter	HD patients without LV DD (n = 43)	HD patients with LV DD (n = 31)	Control group (n = 35)
MMP1, ng/ml	47.7 ± 13.2	101.1 ± 10.4*	46.5 ± 26.1
MMP2, ng/ml	1216.1 ± 189.8	2519.0 ± 233.9**	1186.9 ± 64.0
Tissue inhibitor of MMP1, ng/ml	73.9 ± 11.3	157.1 ± 35.4***	71.9 ± 7.5

Note: *$p = 0.047$, **$p = 0.034$, ***$p = 0.002$ when comparing patients with and without LV DD; HD: hypertensive disease; LV DD: left ventricular diastolic dysfunction; MMP1 and MMP2: type 1 and type 2 matrix metalloproteinases.

the Research Institute of Molecular Medicine of the Chita State Medical Academy on an automatic enzyme immunoassay analyzer using ready-made sets AbFron-tiershuman MMP-1 ELISA, Quantikine 2 MMP2 Immunoassay R&D Systems (Minneapolis, USA). The ratio of MMP1 and MMP2 to tissue inhibitor MMP1 was studied.

The global longitudinal strain was investigated by the method of the non-Doppler mode of two-dimensional gray-scale strain. The study was performed from the apical approach in the position along the long axis, the LV myocardium was recorded with optimal visualization of all segments, with a frame rate of 50 to 80 per sec with stable electrocardiography registration. The endocardium was clearly traced, and the epicardial surface was automatically traced. The program automatically calculated the displacement of the pattern of spots within the zone of interest from frame to frame throughout the entire cardiac cycle. After the zone of interest optimization, the software generated strain curves for each segment.

Statistical data processing was performed using the Statistica 6.0 software. The normal distribution of samples was assessed using the Shapiro–Wilk W-test. Differences were considered statistically significant at p-values of <0.05. The Mann–Whitney U-test was used to compare two sets of continuous independent data, with the correction of the obtained p-values using the Benjamini–Hochberg test due to the multiple comparison procedure. Multiple continuous-type data samples were analyzed using the Kruskal–Wallis H test. Correlation analysis was performed using the Spearman test, which takes into account the abnormal nature of the distribution of samples. The data in the work were presented as the arithmetic mean and standard deviation (Mean ± SD).

Results and discussion. The level of MMP1 revealed an increased value of this indicator by 46% in the group of patients with HD in combination with impaired myocardial relaxation in the diastole phase compared with the group of patients without impaired diastole. Concurrently, no significant differences were found in this indicator between group 1 and the control group of patients (Table 1).

Differences were also revealed in the groups of patients who were examined by the MMP2 level. Group 2 had an increased concentration of this indicator by 47% compared with the group and by 53% compared with the control group (Table 1).

A study by C. Laviades et al. revealed that the level of MMP1 in healthy people and patients with stage 1 HD, as in our study, did not significantly differ [9]. However, these authors showed that the concentration of MMP1 tissue inhibitor was higher in patients with LV hypertrophy in the presence of HD. This is probably due to the inadequate cleavage of collagen against its increased synthesis.

Our study revealed a higher tissue inhibitor MMP1 level in patients HD having LV DD by 42% compared with the group of patients without DD. Concurrently, no statistically significant differences were found between group 1 and the control group (Table 1). The MMP1 and MMP2 ratio to the tissue inhibitor of MMP1 revealed no significant difference between the groups ($p = 0.623$).

The study of echocardiographic parameters (Table 2) revealed a slight increase in the LVMM index in patients with HD having increased disease stages (in group 2, this indicator was higher by 7.2% than in group 1, $p > 0.5$).

The study of global longitudinal myocardial strain depending on the presence of DD (Table 2) showed that in patients with HD having LV DD, this indicator was 22.8% lower than those without DD ($p = 0.048$). Compared with the control, a decreased global longitudinal strain of the myocardium by 23.3% and 40.7% was recorded in groups 1 and 2, respectively ($p = 0.035$ and $p = 0.008$). Our data are consistent with the conclusions of the study of myocardial strain by O.A. Marsalskaya et al. [10]. Currently, global longitudinal strain is considered an early marker of systolic dysfunction of the LV myocardium in patients with HD [10, 11].

Due to increased blood pressure, remodeling occurred with an increased LVMM, which was more pronounced in the group of patients with LV DD. With LV hypertrophy, a strain of the cardiomyocytes, as well as arterioles that feed the myocardium, occurs. Thus, the myocardial stiffness

Table 2. Cardiohemodynamic parameters in patients with hypertensive disease.

Indicator	Group 1, patients with hypertensive disease without diastolic dysfunction of the left ventricle	Group 2, patients with hypertensive disease and diastolic dysfunction of the left ventricle	Group 3, control
Left atrial volume index, ml/m^2	31.1 ± 3.2	36 ± 1.1*	29 ± 1.7
The relative wall thickness of the left ventricle	0.4	0.45	0.35
Flow rate of tricuspid regurgitation, mm/s	242.41 ± 21.71	261.12 ± 5.07	220.33 ± 15.48
Global longitudinal strain of the left ventricle	16.90 ± 2.08*	12.96 ± 1.62	21.89 ± 0.64*
Heart rate	71.50 ± 8.28	71.70 ± 3.82	73.67 ± 6.08
Left ventricular myocardial mass index, g/m^2	94.21 ± 31.30	101.25 ± 20.40	81.30 ± 8.78
Left ventricular filling pressure (E/Em)	9.25 ± 1.24	10.56 ± 3.07	6.37 ± 0.88*

Note: *$p > 0.005$ compared to the control group.

increases [11–13]. As a result, decreased velocities on the annulus fibrosus of the mitral valve were registered due to increased myocardial stiffness of the interventricular septum and LV walls. Therefore, a change in the global longitudinal LV strain was an early sign of impaired myocardial contractility in patients with HD in combination with impaired diastolic relaxation.

The issues of heart failure formation and progression with preserved ejection fraction in patients with HD remain unclear. Therefore, a correlation analysis of the relationship between the MMP level and the above echocardiographic indicators was performed. A moderate negative relationship was established between global longitudinal LV strain and MMP2 ($r = -0.64$, $p < 0.05$), which confirms the opinion about the contribution of MMP2 to the development of systolic dysfunction in patients with HD.

The revealed correlation of global longitudinal LV strain only with MMP2 was due to the absence of high LVMM index values in patients with HD since early, preclinical signs of systolic dysfunction in this category of patients were required.

Thus, considering the above results, a more detailed preventive examination is required in patients with HD, including not only standard echocardiography, but also the study of the global longitudinal strain of the LV, the annulus fibrosus velocity of the mitral valve at the interventricular septum level, as well as MMP1, MMP2, and tissue inhibitor of MMP1.

CONCLUSIONS

1. In patients with HD in combination with LV DD, a decreased global longitudinal strain of the left ventricular myocardium is associated with the MMP2 level.

2. The tissue inhibitor of MMP1 is not associated with the global strain of the LV myocardium.

Author contributions. T.V.K. collected the material, reviewed the literature, analyzed the data obtained, and wrote the text; N.V.L. created the concept and design of the study; M.V.Ch. performed diagnostic tests.

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