FEATURES OF VIOLATIONS OF THE DIASTOLIC FUNCTION OF THE LEFT VENTRICLE IN PATIENTS WITH CHRONIC HEART FAILURE, DEPENDING ON THE CLINICAL COURSE OF THE DISEASE

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ABSTRACT
The aim of our study was to study the features of impaired left ventricular diastolic function in patients with chronic heart failure, depending on the clinical course of the disease.
A total of 131 patients with CHF of ischemic origin with I, II and III FC CHF (men aged 38-60 years, mean age 54.51 ± 6.89 years) were examined. Patients with FC I were 31 (23.7%) patients, with FC II - 51 (38.9%) and FC III - 49 (37.4%) patients. The structural and functional state of the myocardium and the process of LV remodeling were assessed by echocardiography with Doppler ultrasonography. EchoCG was performed on the device "MEDISON ACCUVIX V20" (South Korea), using a 3.25 MHz transducer in standard echocardiographic positions, transthoracic method in accordance with the recommendations of the American Society of Echocardiography (ASE). In patients with CHF, diastolic function disorders were identified in 74.8% of cases: grade I (impaired relaxation) was recorded in 38.9% (51 patients), grade II - (pseudonormal) in 21.4% (28), type III (reversible restrictive) - in 14.5% (19) patients. An analysis of the grades of diastolic dysfunction showed the predominance of relaxation disorders in 52% of patients and an increase in the number of patients with restrictive type of diastolic dysfunction with an increase in CHF FC. Thus, in 74.8% of CHF patients, impaired LV diastolic function was observed, characterized by its deterioration with the progression of the disease. At the same time, impaired LV diastolic function was characterized to a greater extent by impaired relaxation, and with the progression of the disease, a restrictive type of LVDD impairment.
Keywords chronic heart failure, left ventricle, diastolic dysfunction

1. INTRODUCTION

Diastole, in the cardiac cycle, period of relaxation of the heart muscle, during this period the heart muscle is perfused [1]. It is generally accepted to divide diastole into four phases: isovolumetric relaxation: from closure of the aortic valve to opening of the mitral valve; early rapid filling: transmitral pressure gradient drives LV filling; diastasis: period of low flow in mid-diastole; late rapid filling: atrial contraction [2]. In accordance with the broad definition, isolated diastolic dysfunction is a violation of isovolumetric relaxation of the ventricles and a decrease in the elasticity of the left ventricle.

In the presence of diastolic dysfunction, the heart is able to provide the metabolic needs of the body, both at rest and during exercise, but due to an increase in the filling pressure of the left ventricle [3]. With moderate diastolic dysfunction, the late phase of diastolic filling is lengthened until the left ventricular end-diastolic volume returns to normal. In severe diastolic dysfunction, the ventricle becomes so rigid that the atrial myocardium is unable to compensate for filling disturbances and end-diastolic volume cannot be normalized by increasing filling pressure [4]. Therefore, stroke volume and cardiac output decrease and exercise tolerance worsens [5].

Traditionally, CHF is associated with impaired myocardial contractile function. However, according to modern ideas about the pathophysiology of CHF syndrome, DM is considered only as one of the factors along with changes in wall tension and the structure of diastolic filling, i.e. with everything that is included in the concept of "LV remodeling" [6]. In recent years, data on the great importance of diastolic dysfunction (DD) in the onset, clinical course and prognosis of CHF are increasingly encountered.

Numerous studies have been devoted to the study of the effect of LV diabetes mellitus on the prognosis in patients with coronary artery disease [7], the effect of LV DD has been studied much less [8].

In addition, some studies [9] showed that in 30–40% of patients with CHF, the clinic of heart failure is caused by impairments not of systolic, but of diastolic LV function.

There are three main grades of LV diastolic dysfunction - hypertrophic, pseudonormal and restrictive [5]. The latter has the worst prognosis in patients with CHF. With the restrictive grade of DD, LV remodeling reaches such an extent that diabetes mellitus no longer plays a major role, as in the initial stages of CHF formation [10]. The restrictive grade of impaired LV diastolic filling is the most important predictor of cardiovascular mortality and involuntary heart transplantation [11].

2. METHODS

A total of 131 patients with CHF of ischemic origin with I, II and III FC CHF (men aged 38-60 years, mean age 54.51 ± 6.89 years) were examined. The duration of myocardial infarction ranged from 3 months up to 4 years. The diagnosis was established according to the data of clinical and laboratory-instrumental studies. The patients were divided into FCs according to the New York Heart Association (NYHA), according to the six-minute walk test (6MWT). The clinical condition of the patients was determined by the clinical assessment scale of the patients. The clinical characteristics of the patients included in the study are presented in Table 1.

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Patients with FC I were 31 (23.7%) patients, with FC II - 51 (38.9%) and FC III - 49 (37.4%) patients. In 91 (69.5%) patients, hypertonic disease (HD) was diagnosed, the prescription of which was 6.9 ± 3.1 years.

Table 1
Clinical characteristics of patients

Indicators	Parameters
Age (years)	54,51 ± 6,8
CHF FC I II III	 31(23,7%) 51 (38,9 %) 49 (37,4%)
Duration of myocardial infarction (year)	3,23±1,5
Duration of CHF (year)	2,3±0,9
Arterial hypertension (AH)	91 (69,5%)

The structural and functional state of the myocardium and the process of LV remodeling were assessed by echocardiography with Doppler ultrasonography. EchoCG was performed on the device "MEDISON ACCUVIX V20" (South Korea), using a 3.25 MHz transducer in standard echocardiographic positions, transthoracic method in accordance with the recommendations of the American Society of Echocardiography (ASE). Evaluation of LV diastolic function by determining indicators: flow parameters including the early (E) and late (A) diastolic filling velocities, the E/A ratio, and the E deceleration time (DT) (ms), isovolumic relaxation time (IVRT) (ms) of left ventricle. Indicators of LV diastolic function and impaired diastolic function were assessed according to the criteria presented in Table 2.

In accordance with the recommendations [12], there are 3 grades of violations of the diastolic function of the LV myocardium: grade I - impaired relaxation (hypertrophic) (decrease in peak E, ratio E / A <1; DT> 200 ms); grade II - pseudonormal (E> A, E / A> 1, DT - 150-200 ms); III - reversible restrictive grade of filling LV diastole (E / A> 2; DT <150ms, IVRT <60ms).

Table 2
Evaluation criteria for diastolic dysfunction

Indicators	Normal	Options of diastolic dysfunction		
		Impaired relaxation	Pseudonormal	Reversible restrictive
The main				
Peak velocity of E wave	79±26 sm/s	<53 sm/s	N	Increase
Peak velocity of	48±2	>70	N	Decrea

A wave	2 sm/s	sm/s		se
The E/A ratio	1,7±0,6	E/A<1	> 1	> 2
Early left ventricular filling deceleration time, DT	184±24 ms	>200 ms	150-200 ms	< 150 ms
Isovolumic relaxation time of the left ventricle, IVRT	74±7 (60–88) ms	> 100 ms	< 100 ms	< 60 ms

3. STATISTICAL ANALYSIS

The data obtained by us during the study were subjected to statistical processing on a Pentium-IV personal computer using the Microsoft Office Excel - 2013 software package, including the use of built-in statistical processing functions, as well as using the STATISTICA-6.0 software package. Methods of variational parametric and nonparametric statistics were used with the calculation of the arithmetic mean of the studied indicator (M), standard deviation (SD), standard error of the mean (m), relative values (frequency,%), the statistical significance of the measurements obtained when comparing the mean values was determined by the distribution Student's t (t) with the calculation of the error probability (P) when checking the normal distribution (by the kurtosis criterion) and the equality of the general variances (the Fisher's F test). The level of reliability $p < 0.05$ was taken as statistically significant changes. When comparing groups by qualitative characteristics, we used the $\chi 2$ criteria. To study the relationship between quantitative variables, correlation analysis was used with the calculation of the Pearson's linear correlation coefficient.

4. RESULTS

Analysis of the baseline indicators of diastolic function in patients with CHF showed that disorders of diastolic function were initially identified in 74.8% (98 patients) of patients with CHF. At the same time, Grade I (impaired relaxation) was recorded in 38.9% (51 patients), Grade II - (pseudonormal) in 21.4% (28), Grade III (reversible restrictive) - in 14.5% (19) patients (Figure 1).

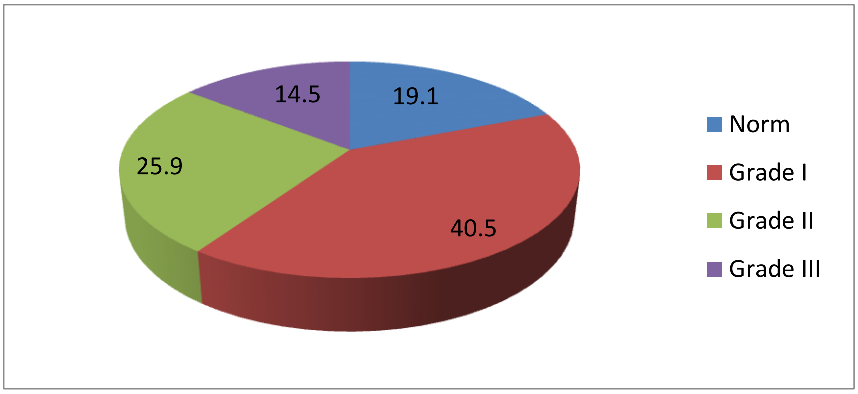

Figure 1 Analysis of violations of LV diastolic function in patients with CHF (%) (grade I (impaired relaxation, grade II - pseudonormal and grade III -reversible restrictive).

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An analysis of the types of violations of diastolic dysfunction depending on the CHF FC showed that in patients with CHF FC I, diastolic dysfunction was identified in 58.1% (18) patients, while only grade I (impaired relaxation) was identified - in 12 patients (38.7%) and grade II - (pseudonormal) in 6 patients (19.4%). In patients with FC II CHF, LV DD was detected in 39 patients (76.5%): grade I (impaired relaxation) - in 22 (43.1%) patients, grade II - (pseudonormal) in 10 (19.6 %) patients, grade III (reversible restrictive) - in 7 (13.7%) patients. In patients with FC III CHF, DD was detected in 83.7% (41 patients) of patients: grade I (impaired delayed relaxation) - in 17 (34.7%) patients, grade II - (pseudonormal) - in 12 (24.5 %) and grade III (reversible restrictive) - in 12 (24.5%) patients (Figure 2).

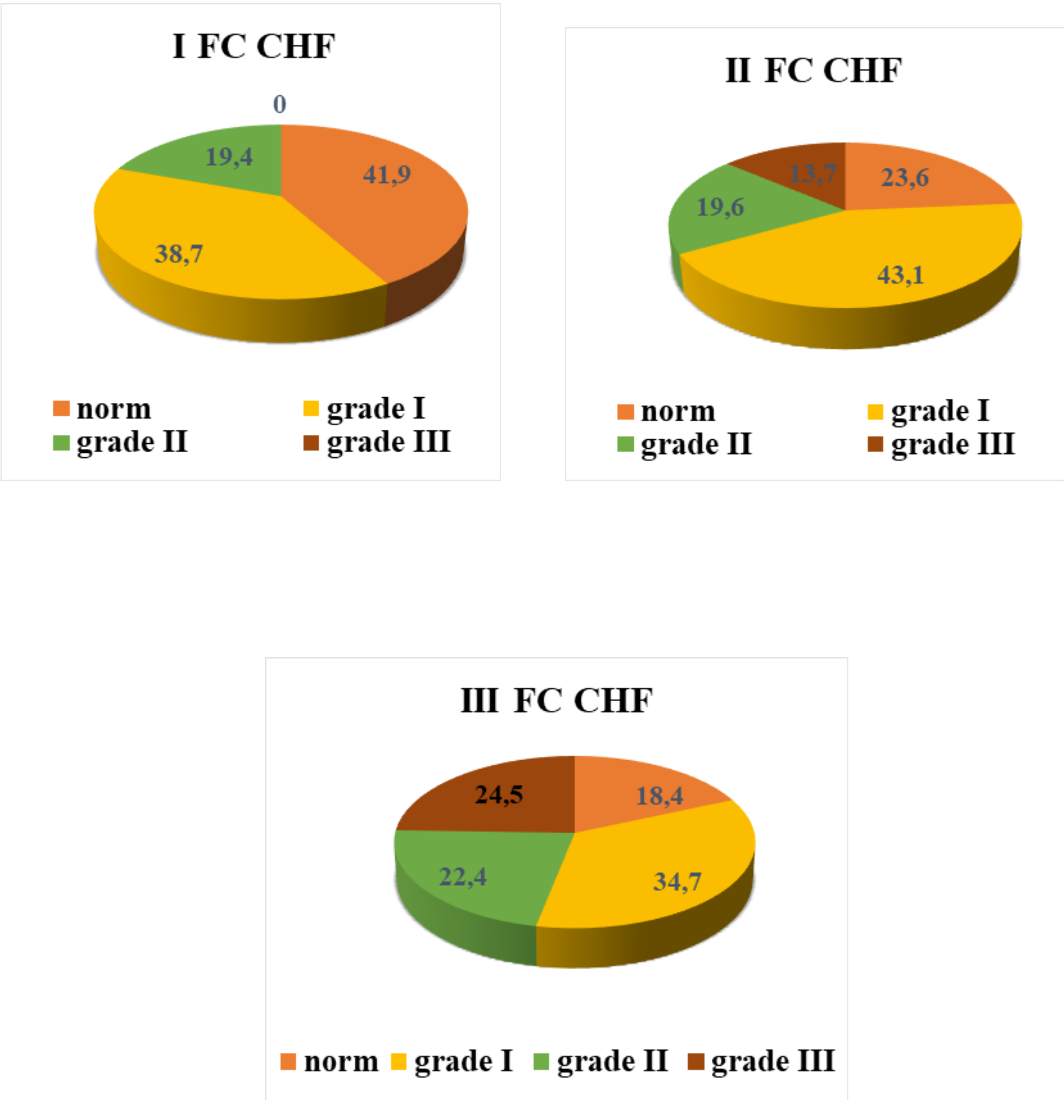

Figure 2 Indicators of distribution of LVDD types in patients with FC I-III CHF (%).

Disorders of LV diastolic function covered both velocity and time parameters of diastole. In the examined patients with CHF, a change in the indicator of the maximum *LV filling* rate in *early* diastole (E), a significant decrease in the time of LV isovolumic relaxation (IVRT) and the flow rate of the in the phase *early left ventricular filling deceleration time*

(DT, ms) is associated with the progression of CHF and an increase in the FC of the disease. The analysis of indicators depending on the FC of CHF showed that the maximum speed of early filling E of the LV with I, II, III FC was 48.9 ± 8.42, 62.1 ± 7.42 and 71.2 ± 9.03 m / s. The time of isovolumic relaxation of the LV - IVRT was 108.5 ± 11.2, 94.6 ± 14.3 and 80.1 ± 16.4 ms with a significant decrease in patients with FC II and III CHF by 12.8% ($p < 0.05$) and 26.2% ($p <0.01$), respectively, compared with the indicators of FC I CHF. The deceleration time of the flow rate in the phase of early LV filling (DT, ms) in patients with FC I, II, III was 212.2 ± 13.25, 184.4 ± 21.91 and 168.3 ± 29.54 ms, respectively. significant decrease in patients with II and III FC CHF by 12.8% ($p <0.05$) and 26.2% ($p <0.01$), respectively, compared with the indicators of FC I CHF.

Thus, the analysis of the types of diastolic dysfunction showed the predominance of relaxation disorders in patients with CHF, an increase in the number of patients with LV DD and an increase in the number of patients with a restrictive type of diastolic dysfunction with an increase in CHF FC.

The analysis of the clinical course of the disease in the examined patients with I, II and III FC CHF showed: the initial indicators of 6MWT were 464.3 ± 30.15, 348.6 ± 29.41 and 231.5 ± 32.27 meters, respectively. In patients with CHF II and III FC CHF, a decrease in exercise tolerance was characterized by a decrease in the 6MWT distance by 24.9% ($p <0.05$) and 50.17% ($p <0.001$), respectively, compared with the 6MWT indicators in patients with I FC CHF. The study of the initial indicators of the clinical state of patients with CHF according to the results of clinical assessment scale revealed that the indicators in patients with CHF I, II and III FC were 3.48 ± 0.69; 6.14 ± 0.57 and 11.27 ± 0.79 points, respectively.

The analysis of the initial indicators of the quality of life according to the total index of the quality of life according to the results of the Minnesota Satisfaction Questionnaire (MSQ) in the examined patients showed a significant increase in summary quality-of-life indices with an increase in the FC of CHF. In patients with FC I, II, and III of CHF, summary quality-of-life indices was 24.6 ± 2.9, 35.1 ± 2.6 and 45.7 ± 3.4 points, respectively, with a significant increase in summary quality-of-life indices in patients with II and III FC CHF by 42.7% ($p <0.01$) and 85.8% ($p <0.001$), respectively, compared with the indicators of patients with FC I CHF.

An analysis of the 6MWT, clinical assessment scale, and QOL indicators in CHF patients depending on the types of LVDD showed significant differences in these indicators between the grades of LVDD. In patients with grade I LVDD, the indices of 6MWT and clinical assessment scale were 431.6 ± 39.48 meters and 5.4 ± 2.54 points. In patients with grade II, these indicators were 361.7 ± 33.1 meters and 7.9 ± 2.25 points and grade III 224.8 ± 31.61 meters 11.8 ± 2.31 points, respectively.

An analysis of the 6MWT and clinical assessment scale indicators in CHF patients depending on the grades of LVDD showed significant differences in these indicators between the types of LVDD. In patients with grade I LVDV, the indicators of clinical assessment scale and 6MWT were 6.7 ± 2.25 points and 424.5 ± 48.71 meters. In patients with grade II, the sum of the scores of clinical assessment scale and 6MWT was 8.7 ± 2.0 points 338.2 ± 51.2 meters and grade III 10.4 ± 2.0 points 203.61 ± 42.45 meters, respectively (Figure 3).

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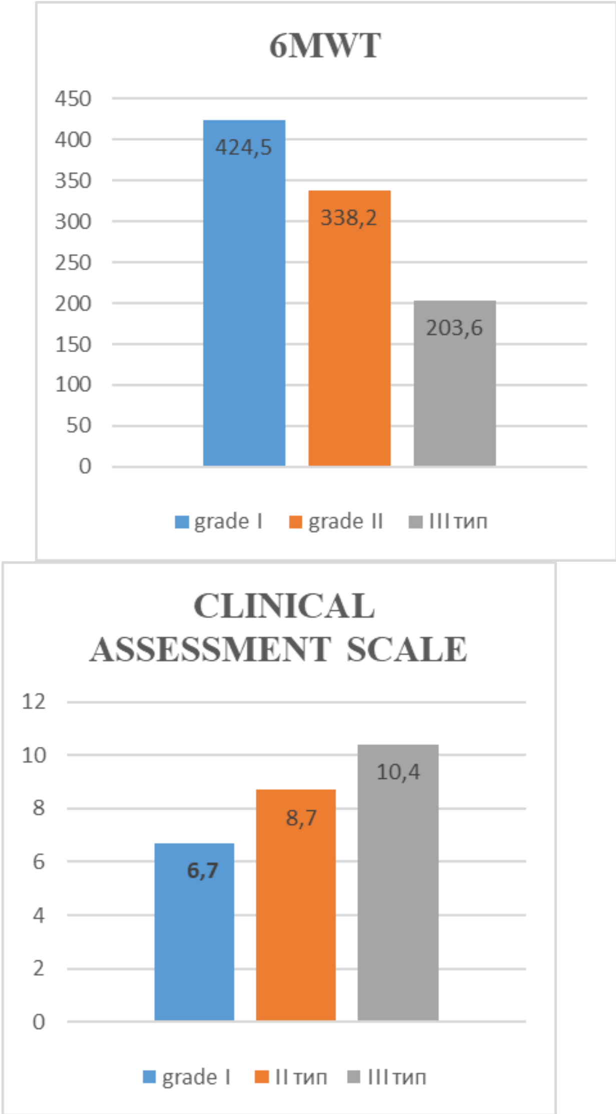

Figure 3 Indicators of 6 MWT and clinical assessment scale in patients with different grades of LVDD.

Thus, in patients with CHF, diastolic function disorders were identified in 74.8% of cases: grade I (impaired relaxation) was recorded in 38.9% (51 patients), grade II - (pseudonormal) in 21.4% (28), grade III (reversible restrictive) - in 14.5% (19) patients. Analysis of the grades of diastolic dysfunction showed the predominance of relaxation disorders in 52% of patients and an increase in the number of patients with restrictive grade of diastolic dysfunction with an increase in CHF FC (Figure 4).

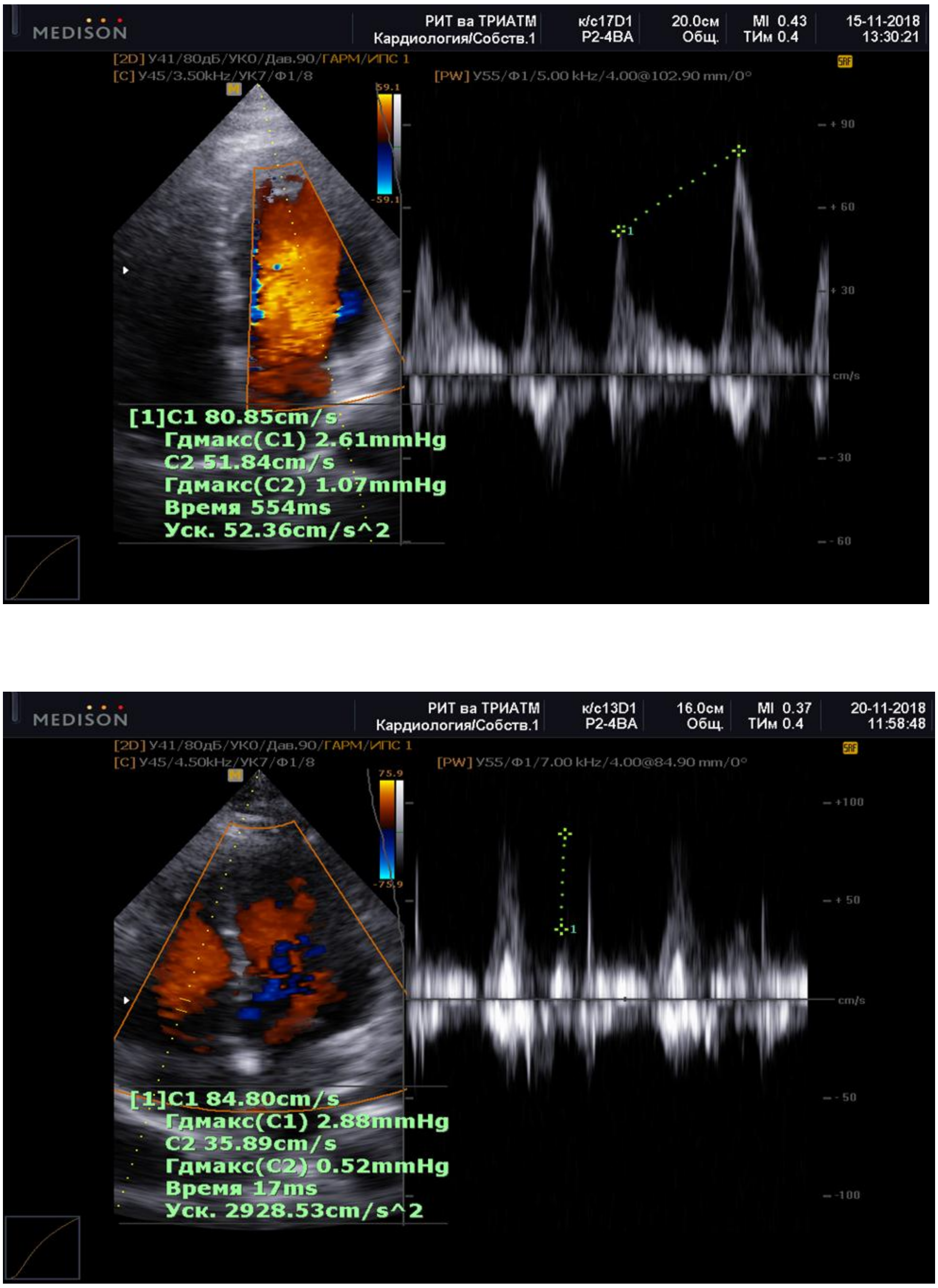

Figure 4 Grade II DDLV in patients with CHF.

Severe impairments of left ventricular diastolic function - pseudonormal and restrictive grades were significantly more frequent in the group of patients with reduced LV systolic function (EF <40%) and a relationship was found between disease progression and an increase in volumetric parameters - end-diastolic and end-systolic LV volumes with restrictive grade of diastolic dysfunction. With the progression of the disease in CHF (FC III), there was an increase in the number of patients with an eccentric type of remodeling and a restrictive grade of LVDD.

5. DISCUSSION

Early diastole begins with the period of isovolumic relaxation of the ventricle and leads to equalization of pressure between the atrium and the ventricle, which in turn depends on the pressure in the atrium itself and the rate of relaxation of the ventricular myocardium. The most common cause of DD is impaired myocardial contractility. The main pathogenetic factors that contribute to the development of DD include myocardial fibrosis, its hypertrophy, ischemia, as well as an increase in afterload in arterial hypertension. The most important consequence of the interaction of these factors is an increase in the concentration of calcium ions in cardiomyocytes, a decrease in LV myocardial compliance, impaired relaxation of the heart muscle, a change in the normal ratio of early and late LV filling, and an increase in the end-diastolic volume [13].

The relaxation process is determined by the rate of actin-myosin dissociation (active, energy-dependent part of relaxation) and stretching of the elastic structures of the myocardium, compressed during systole (passive, non-volatile part of relaxation) [14]. The rate of dissociation depends on the affinity of the troponin C protein to Ca^{2+} ions and the calcium concentration in the free space around myofilaments and in the sarcoplasmic reticulum. The regulation of the concentration of Ca^{2+} ions, in turn, is provided by the operation of the transmembrane and sarcoplasmic calcium pump (Ca^{2+} ATPase), and the very process of pumping ions into the reticulum, especially against the concentration gradient, requires a significant amount of free macroenergetic phosphates [15].

In this regard, it seems most likely that it is the energy-intensive process of Ca^{2+} absorption by the reticulum that is the weak link that is disturbed in cardiac pathology and initiates DD [3,26]. It should be noted that the energy intensity of calcium inactivation significantly exceeds the energy consumption for its delivery to myofilaments, which makes diastole an earlier and more vulnerable target in any disease accompanied by energy deficiency, especially in myocardial ischemia. Probably, this serves as a biochemical basis for the fact that in primary myocardial damage, diastole disturbance precedes systolic dysfunction [13,16].

H. Dokainish et al. (2008) [17] showed that the parameters of spectrum of the transmitral diastolic flow closely correlate with the severity of CHF. The widespread use of the method is associated with the availability and ease of implementation, when the dynamics of only one parameter Ve / Va, one can judge the diastolic function of the LV as a whole. Therefore, the relationship between violations of LV diastolic filling, clinical manifestations of decompensation and the patient's functional status is currently the subject of in-depth research [18]. It is important to note that the relationship of the functional class of CHF with the indicators of DD is significantly higher than with the parameters of systolic function and, in particular, with EF [19]. It has been proven that with a gradual disturbance of energy production, the relaxation of the isolated heart changes earlier than the decrease in the indicators of systolic function. That is why changes in the indicators of LV diastolic filling are considered the earliest markers of the disease, preceding the detailed clinical picture of CHF. Changes in myocardial relaxation indicators in the early preclinical stages of CHF can occur with a relatively stable contraction process [20]. Thus, DD often precedes a violation of systolic function and can lead to the appearance of CHF even in cases where the indicators of central hemodynamics (ejection fraction - EF, stroke volume, cardiac output, cardiac index) have not yet changed. LV DD leads to hemodynamic overload of the left atrium, its dilatation, manifestations of ectopic activity in the form of supraventricular rhythm disturbances - extrasystole, paroxysmal atrial fibrillation. However, in most cases, DD is a single process for both ventricles of the heart, and it is not possible to distinguish clinically to distinguish LV systolic or diastolic function in CHF. That is why the diagnosis of diastolic dysfunction is based solely on the use of instrumental methods.

6. CONCLUSION

Thus, in 74.8% of CHF patients, LV diastolic function disorders were observed, characterized by its deterioration with the progression of the disease. At the same time, impaired LV diastolic function was characterized to a greater extent by impaired relaxation, and with the progression of the disease, a restrictive grade of LVDD impairment.

Conflict of interest: none declared.

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