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EVALUATION OF THE FUNCTIONAL STATE AND FEATURES OF LEFT VENTRICULAR REMODELING IN PATIENTS WITH ACUTE RHEUMATIC FEVER

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The purpose of the study was to identify the features of hemodynamics and structural changes in patients with history of acute rheumatic fever, with and without myxomatous degeneration of the valvular-chordal apparatus. The study included 27 patients aged 15–21 years who had a history of acute rheumatic fever. All patients were divided into 2 groups: group I – patients without myxomatous degeneration; group II – patients with signs of myxomatous degeneration. The comparison group consisted of 14 practically healthy individuals of the appropriate age without a "rheumatic" history and echocardiographic signs of damage to the valvular-chordal apparatus. In patients who had history of acute rheumatic fever, an increase of end-diastolic diameter (by 4.8 %; $p<0.05$) and end-diastolic volume (by 11.9 %; $p<0.05$) of the left ventricle, was observed. Patients who had myxomatous degeneration, were characterized by a significant increase in end-systolic diameter (by 16.7 %; $p<0.001$) and end-systolic volume (by 45.1 %; $p<0.001$), as well as a decrease in ejection fraction (16.8 %; $p<0.001$). In patients with rheumatic heart disease, left ventricle myocardial remodeling was observed: in myxomatous degeneration – concentric variant was revealed, without myxomatous degeneration – an eccentric variant. So, in patients with acute rheumatic fever, due to compensatory mechanisms, changes in the geometry of the left ventricle occur, which become maladaptive in the presence of myxomatous degeneration.

Key words: acute rheumatic fever, myxomatous degeneration, concentric and eccentric remodeling

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ОЦІНКА ФУНКЦІОНАЛЬНОГО СТАНУ І ОСОБЛИВОСТЕЙ РЕМОДЕЛЮВАННЯ ЛІВОГО ШЛУНОЧКА У ХВОРИХ НА ГОСТРУ РЕВМАТИЧНУ ЛИХОМАНКУ

Метою дослідження було виявити особливості гемодинаміки та структурних змін у хворих з гострою ревматичною лихоманкою з міксоматозною дегенерацією та без неї. До дослідження було включено 27 пацієнтів віком 15–21 рік, які перенесли гостру ревматичну лихоманку. Хворі були поділені на 2 групи: I група – хворі без міксоматозної дегенерації; II група – хворі з міксоматозною дегенерацією. Групу порівняння склали 14 практично здорових осіб без ревматичного анамнезу. У пацієнтів, які перенесли гостру ревматичну лихоманку, спостерігається збільшення кінцево-діастолічного розміру (на 4,8 %; $p<0,05$) та кінцево-діастолічного об'єму (на 11,9 %; $p<0,05$). Пацієнти з міксоматозною дегенерацією характеризувалися достовірним збільшенням кінцево-систолічного розміру (на 16,7 %; $p<0,001$) та кінцево-систолічного об'єму (на 45,1 %; $p<0,001$) лівого шлуночка, а також зниженням фракції викиду (16,8 %, $p<0,001$). У обстежених пацієнтів спостерігалося ремоделювання міокарда лівого шлуночка: при міксоматозній дегенерації – концентричний варіант, за відсутності міксоматозної дегенерації – ексцентричний. Отже, у пацієнтів з ревматичною хворобою серця за рахунок компенсаторних механізмів відбуваються зміни геометрії лівого шлуночка, які набувають дезадаптивного характеру за наявності міксоматозної дегенерації.

Ключові слова: гостра ревматична лихоманка, міксоматозна дегенерація, концентричне та ексцентричне ремоделювання.

At the present stage, the assessment of the features of cardiac disorders and the prediction of the development of complications cannot be considered complete without determining the characteristics of hemodynamics and structural changes in the heart [1, 2, 3]. At the same time, along with the traditional study of hemodynamic parameters, much attention is paid to the identification of remodeling options. Under "remodeling of the heart" a complex of changes in the structure and geometry of the heart chambers is understood, including both damaged and undamaged areas of the myocardium. Often, these changes precede the clinical manifestation of heart failure, and in some cases, myocardial restructuring can independently exacerbate systolic and diastolic ventricular dysfunction [6].

It is especially important to identify such structural changes in cardiovascular pathology, which in the vast majority of cases is characterized by a residual lesion of the valvular-chordal apparatus of the heart. Acute rheumatic fever (ARF) and chronic rheumatic heart disease (RHD) can be attributed to such a pathology, when disorders that occur during the acute period, gradually aggravating, lead to a formed pathology in the catamnesis [15]. There were approximately 471,000 cases of ARF each year [4]. The Global Burden of Disease (GBD) study more recently estimated that there are 33 million prevalent cases of RHD, causing more than 9 million Disability-Adjusted Life Years lost and 275.000 deaths each year [5]. All this indicates the relevance of the studied pathology.

It is considered that the presence of myxomatous degeneration (MD) of the heart may worsen the course of other cardiac pathologies and contribute to the development of more severe complications [8]. Myxomatous degeneration of the cardiac valves stands for the non-inflammatory progressive disarray of the valve structure caused by a defect in the mechanical integrity of the leaflet due to the altered synthesis and/or remodeling by collagen [14]. Common alterations include fragmentation of the collagen of the fibrosa layer, and the presence of disrupted, fragmented, and granular elastic fibers forming an amorphous clump. Myxoid infiltrating lesions in the marginal region were mainly comprised of collagen I and V, whereas lesions in the central region were found to be mainly collagen I and III. Myxomatous degeneration in 38 % of cases extends to the chordal apparatus, and sometimes it can involve the conduction system of the heart and intracardiac nerve fibers. Macroscopically, the valve leaflets look thickened, enlarged, "swollen" [8, 14].

Obviously, the combination of such pathologies, which are quite significant in terms of complications, dictates the need to identify early signs of impending irreversible disorders.

The purpose of the study was to identify the features of hemodynamics and structural changes in patients with a history of acute rheumatic fever, with and without myxomatous degeneration of the valvular-chordal apparatus.

Materials and methods. The study included 27 patients aged 15–21 years (mean age 17.8±1.9 years) who had a history of ARF. All patients were divided into 2 groups depending on the presence or absence of signs of MD: group I (n=15) – patients who had ARF, without MD; group II (n=12) – patients with a history of ARF, with signs of MD of the valvular-chordal apparatus. The comparison group consisted of 14 practically healthy individuals of the appropriate age without a "rheumatic" history and echocardiographic signs of damage to the valvular-chordal apparatus.

To assess the state of the valvular apparatus of the heart and indicators of cardiohemodynamics, the one-dimensional and two-dimensional echocardiography (ECHOCG) were used, as well as Doppler echocardiography in a pulsed wave mode with the position of the gated volume in the region of the inflow tract of the left ventricle. The examination was performed with the patient lying on his back and left side in the parasternal, apical and subcostal approaches.

The following indicators were determined: aortic diameter (AD), left atrial diameter (LAD), end-systolic diameter (ESD) and end-diastolic diameter (EDD) of the left ventricle (LV), LV end-systolic volume (ESV) and end-diastolic volume (EDV), ejection fraction (EF) of the left ventricle, stroke (SV) and minute (MO) volumes of blood circulation, the thickness of the posterior wall of the left ventricle in diastole (LVPWDT), the thickness of the interventricular septum in diastole (IVSDT), mitral orifice area (MOA) .

In addition to the main linear and volumetric ECHOCG parameters, such indicators as the relative thickness of the posterior wall of the left ventricle (RLVPWT), the relative thickness of the interventricular septum (RIVST), relative wall thickness (RWT) were evaluated and correlated them with the mass of the left ventricular myocardium (LVMM).

The presence of MD leaflets was determined using the criteria of T. Takamoto [13]: thickening of the leaflet by 4 mm or more with a decrease in its echo density compared to the aorta.

The obtained digital data were subjected to statistical processing by biometric methods using the Statistica 10.0 package. To assess the statistical difference between the quantitative values of the variational series, the nonparametric U-test of Wilcoxon (Mann-Whitney) was used. Differences were considered significant at $p<0.05$

Results of the study and their discussion, Echocardiographic examination revealed changes in the valves of various nature in all patients (100.0 %). In this connection, it was possible to talk about RHD in the examined patients. The changes concerned mainly the mitral valve. So, in 16 (59.3 %) patients, secondary mitral valve prolapse was detected (no history), in 6 (22.2 %) patients – mitral insufficiency with mitral regurgitation of I–II degree, in 3 (11.1 %) patients – mitral stenosis, and only 2 (7.4 %) patients had signs of aortic insufficiency. Analyzing the data obtained during the examination of patients who had the history of ARF, we encountered both ambiguous changes in indicators characterizing the systolic function of the left ventricle, and various variants of left ventricular myocardial remodeling. Echocardiographic parameters in the examined patients are shown in Table 1.

In the examined patients, we observed an increase in linear and volumetric parameters of the left ventricle. Thus, the EDD (by 4.8 %; $p<0.05$) and EDV (by 11.9 %; $p<0.05$) of the left ventricle were significantly higher than in the control. At the same time, there was a tendency to increase ESD (by 5.8 %), EDV (by 14.3 %). These changes are, in our opinion, a sign of the emerging myocardial overload, which is confirmed by an increase in MV (by 14.8 %; $p<0.05$) in these patients.

Table 1

Echocardiographic parameters in patients with RHD

ECHOCG parameters	Control group (n=14)	Group I (n=15)	Group II (n=12)
AD (cm)	2.86±0.08 (2.5–3.2)	2.89±0.07 (2.4–3.3)	3.11±0.10* (2.6–3.7)
LAD (cm)	2.76±0.05 (2.6–3.2)	2.98±0.05* (2.4–3.5)	3.31±0.12*** (2.8–3.7)
EDD (cm)	4.69±0.10 (4.1–4.9)	4.81±0.04* (4.2–5.2)	4.63±0.02 (4.0–4.8)
ESD (cm)	2.68±0.06 (2.4–3.0)	2.59±0.09 (2.3–3.2)	3.27±0.08*** (2.5–3.9)
LVPWDT (cm)	0.74±0.08 (0.5–0.8)	0.77±0.09 (0.6–0.9)	0.82±0.04** (0.8–1.1)
IVSDT (cm)	0.66±0.02 (0.4–0.9)	0.71±0.03* (0.5–0.9)	0.87±0.02*** (0.7–1.2)
EDV (ml)	86.3±2.6 (71.5–98.6)	93.4±2.0* (84.2–108.5)	89.7±3.6 (73.6–102.2)
ESV (ml)	27.3±1.6 (18.1–37.9)	31.5±2.1 (22.6–41.3)	42.6±2.8*** (24.1–56.3)
SV(ml)	58.4±2.8 (42.3–72.4)	60.3±2.6 (50.8–86.5)	45.8±1.5* (41.1–50.3)
MV (l/min)	4.42±0.15 (3.57–4.13)	4.97±0.16* (4.25–7.33)	3.46±0.08* (3.16–4.35)
EF (%)	69.2±1.7 (58.3–77.4)	65.6±2.2 (53.4–75.1)	53.8±1.4*** (48.4–65.3)
LVMM (g)	96.2±3.88 (72.3–44.2)	117.3±4.8** (96.4–145.7)	127.5±7.7** (98.9–158.0)
MOA (cm^2)	5.01±0.08 (4.3–6.1)	5.23±0.06* (4.5–5.8)	5.36±0.05* (4.8–5.7)

Note: statistically significant difference with the control group: * – p<0.05; ** – p<0.01; *** – p<0.001.

Morphological compensation of such an overload is an increase in IVST (by 11.5 %; p<0.05), LVPWDT (by 7.1 %), LVMM (by 24.2 %; p<0.01), as well as the size of the left atrium (by 11.1 %; p<0.05). The latter is due to the presence in patients of this group of more pronounced mitral regurgitation, than in patients of group II, which creates an additional volume factor.

In the group of patients with signs of MD, there were more pronounced disorders of the functional state of the left ventricle, which was manifested by a significant increase in ESD (by 16.7 %; p<0.001) and ESV (by 45.1 %; p<0.001), a decrease in EF (16.8 %; p<0.001), decrease in MV (by 11.4 %; p<0.05). In addition, there was a significant increase in the values of LVPWDT (by 12.1 %; p<0.01), IVSDT (by 19.4 %; p<0.001), and LVMM (by 30.8 %; p<0.01), compared to control. Higher values of these indicators indicate that the overload of the left parts of the heart forms in this case a symmetrical hypertrophy of the left ventricular myocardium.

Based on the obtained echocardiographic parameters, the features of left ventricular remodeling were determined. Structural and geometric parameters of patients, allowing determining the type of left ventricular remodeling, are shown in Table. 2

Table 2

Structural and geometric parameters in patients with RHD

Parameters	Control group (n=14)	Group I (n=15)	Group II (n=12)
RLVPWT(cm)	0.331±0.010 (0.259–0.385)	0.336±0.007 (0.293–0.382)	0.358±0.006* (0.315–0.395)
RIVST (cm)	0.311±0.003 (0.258–0.358)	0.321±0.011 (0.242–0.384)	0.363±0.009*** (0.327–0.398)
RWT (cm)	0.320±0.009 (0.250–0.372)	0.328±0.007 (0.271–0.369)	0.353±0.006** (0.321–0.385)
LVMM (g)	96.2±3.88 (72.3–144.2)	117.3±4.8** (96.4–145.7)	127.5±7.7** (98.9–158.0)

Note: statistically significant difference with the control group: * – p<0.05; ** – p<0.01; *** – p<0.001.

In patients of group I, there was a significant increase in LVMM (by 24.2 %; p<0.01). At the same time, RLVPWT, RIVST, and RWT remained within the normal range. Based on the foregoing, we can speak of a distinct increase in myocardial mass against the background of volumetric hyperfunction of the left ventricular myocardium and its characteristic remodeling with the development of eccentric hypertrophy.

Structural and geometric parameters in the group of patients with signs of MD valve-chordal apparatus significantly differed from the control. At the same time, an increase was observed, as was the wall thickness – RIVST (by 16.1 %; $p<0.001$), RLVPWT (by 8.3 %; $p<0.05$), RWT (by 12.1 %; $p<0.01$), and LVMM (by 30.8 %; $p<0.01$). Thus, in this group of patients, against the background of impaired systolic function, remodeling of the left ventricular myocardium was noted according to the type of concentric hypertrophy, in which sarcomeres are added inside the cardiomyocyte.

Analyzing the obtained data, we came to the conclusion that patients who underwent ARF, depending on the presence or absence of MD, undergo multidirectional structural rearrangement, accompanied by remodeling of the left ventricle.

RHD, both in combination and without MD, contributes to a change in the functional state of the left ventricle. This is evidenced by the results of our study. The same conclusions are found in the works of other authors. Thus, Okello, et al pointed out that atrial fibrillation is uncommon with pure mitral regurgitation, but occurs more commonly as left atrial size increases. They indicate, that over time, mitral regurgitation can result in left ventricular dysfunction and symptomatic patients usually present with signs of left heart failure, decreased exercise tolerance, and shortness of breath with exertion [10].

In our study, there was also an increase in the size of the left atrium, as well as signs of volume overload, which will eventually lead to the development of LV dysfunction. Prolonged MR leads to diastolic dysfunction, which in turn supports LV dilatation. This trend, in our opinion, reflects the morphological rearrangement of the myocardium in response to volume overload, when the increase in the ventricular chamber precedes the thickening of the myocardium [11].

Early detection of MR and LA increase is very important, because some authors indicate that timely surgical treatment can contribute to the regression of pathological changes. So, Levin BR et al., at 3 day post-procedure transthoracic echocardiography follow-up, there was significant improvement in LA size in adult patients with moderate to severe MR who underwent MV surgery (LA size 41 mm pre and 31 mm post, $p<0.001$). They pointed hat LA size also improved in moderate to severe MS patients (LA size 34.4 mm pre, 29.6 mm post, $p=0.012$). LVEDD significantly decreased in size with moderate to severe MR who underwent MV surgery ($p=0.01$ and 0.006) [6]. Although our patient with MR also demonstrated significant increasing of LVEDD, it is logical to consider the possibility of surgical correction in patients with RHD and MR, even without MD.

As mentioned above, MD can significantly complicate the course of concomitant cardiac pathology. This can be evidenced by pronounced signs of a decrease in LV contractility in our patients with a combination of RHD and MD. This is an inevitable result of a violation of the structure of the valvular-chordal apparatus and the myocardium itself, both as a result of a rheumatic inflammatory process and as a result of an initially altered histological structure of the heart tissue [7, 13]. Richards JM et al indicated that mitral valves of rheumatic patients have a higher deposition of collagens Type I and Type III, evidence of fibrosis, which might be result of the high expression of TGF-β by contributing to myofibroblast activation and collagen production [12]. Thus, the combination of MD and inflammatory collagen formation in RHD accelerates the development of heart failure, changes in the geometry of the heart and an unfavorable variant of heart remodeling in the form of concentric hypertrophy. Concentric hypertrophy is considered one of the unfavorable options for LV remodeling, since this form affects the main energy-dependent processes in the myocardium – contraction and relaxation [6]. It is believed that this variant of remodeling is accompanied by the highest risk of developing ventricular extrasystoles and increases the risk of developing chronic heart failure by 15 times [2].

Importantly, afterload reduction has not been shown to slow symptom development, preserve left ventricular function, or improve survival rates. As a result, it is not a recommended course of treatment. Thus, patients who develop symptoms or have decreased left ventricular function should be referred for surgical intervention [9]. Surgical intervention should also be considered in patients with severe left ventricular enlargement but preserved left ventricular function. This also indicates the importance of timely detection of cardiac remodeling in RHD.

Conclusions

1. In patients who had history of ARF, there is an increase in linear and volumetric parameters of the left ventricle (EDD (by 4.8 %; $p<0.05$) and EDV (by 11.9 %; $p<0.05$)), as well as MV (by 14.8 %; $p<0.05$).

2. Patients who, along with RHD, had signs of MD, were characterized by more pronounced disorders of the functional state of the left ventricle: a significant increase in ESD (by 16.7 %; $p<0.001$) and ESV (by 45.1 %; $p<0.001$), as well as a decrease in EF (16.8 %; $p<0.001$) and MV (by 11.4 %; $p<0.05$).

3. Both in the presence and absence of MD in patients with RHD, LV myocardial remodeling was observed, however, in MD, signs of a concentric variant were revealed, but in the absence of MD, an eccentric variant.

The data of our study allow us to conclude that in response to myocardial overload in patients with ARF, compensatory mechanisms are activated, leading to changes in the geometry of the left ventricle, which become maladaptive in the presence of MD.

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