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Clinical significance of different assessment methods of myocardial fibrosis in patients with hypertrophic cardiomyopathy

Objective	To evaluate prospects for clinical use of circulating biomarkers for characterizing fibrotic changes in the myocardium of patients with hypertrophic cardiomyopathy (HCMP) with left ventricular (LV) outflow tract obstruction.
Materials and Methods	This was a prospective study with a 12-month follow-up period. The study included 47 patients (29 females and 18 males) with obstructive HCMP who were selected for septal reduction. Echocardiography (EchoCG), cardiac magnetic resonance imaging (MRI) and measurements of serum C-reactive protein, N-terminal pro-brain natriuretic peptide, and relevant circulating markers of fibrosis (TGF-β1, MMP-2,-9, TIMP-1, galectin-3, sST2, CITP, PICP, and PIIINP) were performed for all patients. All patients were evaluated at baseline and at 7 days, 6 and 12 months following surgical treatment. Morphometrical analysis of intraoperative biopsy samples was performed for evaluation of the degree of fibrotic changes. Patients received beta-blockers (95.7%), angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (34%), loop diuretics (68.1%), aldosterone antagonists (34%), and statins (66%).
Results	Women with HCMP were older and more frequently had additional risk factors (arterial hypertension). Men had a higher risk of sudden cardiac death. Histological study of intraoperative myocardial biopsy samples showed that the area of fibrotic changes was 13.9±6.9%. According to cardiac MRI mean area of delayed contrast enhancement was 8.7±3.3% of LV myocardial mass. No association was established between traditional cardiovascular risk factors and severity of myocardial fibrotic changes or levels of circulating fibrosis markers. Perhaps that was due to the modifying effect of the drug therapy received by HCMP patients. According to EchoCG maximum pressure gradient in the LV outflow tract before the surgical treatment was 88 (55; 192) mm Hg, and interventricular septal thickness was 22 (16; 32) mm. A considerable decrease (p=0.0002) in the LV outflow tract gradient was observed after myectomy in all patients. At the same time, the left ventricular dimension, which tended to decrease in the early postoperative period, returned to baseline values by the 6th month of follow-up.
Conclusion	The study confirmed the increase in relevant circulating markers of fibrosis in patients with obstructive HCMP. At the same time, no correlation was observed between levels of circulating biomarkers and severity of fibrosis according to data of histology and cardiac MRI, which was probably due to the modifying effect of drug therapy and limited sampling.

Keywords	Hypertrophic cardiomyopathy; sudden cardiac death; biomarkers; fibrosis
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Idiopathic hypertrophic cardiomyopathy (HCM) is one of the most common monogenic diseases, and is associated with mutations in the cardiac sarcomere protein gene. There is an opinion that it is myocardial fibrosis rather than pathological hypertrophy of the myocardium that is a source of life-threatening rhythm disturbances and associated sudden cardiac death (SCD), as well as the diastolic and systolic (in the terminal stage) dysfunction of the myocardium. The mechanisms of formation of fibrotic changes in HCM are not fully understood. Myocardial fibrosis is primarily compensatory and is related to the loss of cardiomyocytes due to a disturbance of energy metabolism. The contribution of later changes associated with the obstruction of the left ventricular outflow tract (LVOT) and myocardial ischemia in the presence of microcirculation violations cannot be excluded. However, several experimental studies have shown that profibrotic conditions, which can lead to further fibrotic changes in the myocardium, develop in early-stage HCM before the development of typical

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morphological manifestations [1]. Histological examinations remain the gold standard of the assessment of myocardial stroma. However, in recent years, the severity of fibrotic changes in the myocardium has been assessed widely in clinical practice using the circulating biomarkers based on the measurement of serum peptides, derivatives of fibrillar collagen synthesis, and activity of matrix metalloproteinases (MMPs) and their inhibitors, which unfortunately have extremely low specificity. Hence, new biomarkers are actively being sought; their value for the study of fibrotic changes in the myocardium is yet to be determined.

It was suggested, therefore, to assess within this study prospects for the clinical use of circulating biomarkers to characterize fibrotic changes in the myocardium in patients with HCM and LVOT obstruction.

Materials and methods

The prospective study included 47 (29 female and 18 male) patients with the obstructive form of HCM selected to undergo septal myectomy. The local ethics committee of Almazov National Medical Research Center approved the study protocol. All studies involving individual persons were performed under the principles of the Declaration of Helsinki after obtaining signed informed consent forms.

Clinical characteristics of patients and the study design, respectively, are presented in Table 1 and Figure 1. All patients with hypertension received that diagnosis after the diagnosis of HCM was verified. Table 2 shows the results of instrumental examination. All patients underwent echocardiography using a Vivid 9 ultrasound system (General Electric, USA) under the standard protocol with the assessment of LV diastolic function. Electrocardiogram (ECG) – synchronized magnetic resonance imaging (MRI) of the heart was performed before the surgical intervention using a high-field MRI scanner MAGNETOM Trio A Tim 3.0T (Siemens). MR images were processed using the MR Cardiac Analysis software on a Syngo Via Siemens workstation following the ACCF/ACR/AHA/NASCI/SCMR guidelines [2].

Serum levels of C-reactive protein were analyzed using a turbidimetric method on an automatic biochemical analyzer Cobas Integra 400+. The serum concentration of N-terminal pro-brain natriuretic peptide (NT-proBNP) was estimated by electro-chemiluminescent assay using an Elecsys analyzer (Roche Diagnostic). Serum levels of transforming growth factor-beta 1 (TGF-β1; R&D system), matrix metalloproteinases –2, –9 (DFID-2, DFID-9, R&D system), tissue inhibitor of matrix metalloproteinases-1 (TIMP1, R&D system), galectin-3 (R&D system), soluble ST2 receptor 4 for interleukin 1 (sST2, Clinical Diagnostics, Presage ST2 kit), C-terminal telopeptide of type I collagen (CITP, MyBioSource) as a marker of collagen degradation, and C-terminal propeptide of type I collagen (PICP) (USCN Life Science) and N-terminal propeptide of type III procollagen (PIIINP) (USCN Life Science) as markers of collagen synthesis were determined using an enzyme-

Table 1. Clinical characteristics of patients with HCM

Parameter	All patients, n=47	Female, n=29	Male, n=18
Age, years	55±9	58±9*	52±9
BMI, kg/m²	29±4	29±3	27±5
DM, n (%)	1 (2.1)	1 (3.4)	0 (0)
Hypertension, n (%)	38 (79.2)	26 (87.7)	12 (66.7)
Smokers, n (%)	18 (37.5)	6 (20.7)	12 (66.7)**
Syncope, n (%)	7 (14.9)	2 (6.9)	5 (27.8)
Anginose syndrome, n (%)	9 (18.8)	4 (13.8)	5 (27.8)
AF, abs (%)	7 (14.6)	4 (13.8)	3 (16.7)
CVA, abs (%)	4 (8.3)	1 (3.4)	3 (16.7)
Risk of SCD, %	3.9 (2.4; 4.5)	2.5 (2.4; 3.4)	3.8 (2.8; 5.5)*
NT-proBNP, ng/mL	1,006 (599; 2,019)	1,246 (656; 2,344)	882.6 (469; 1,526)
Beta blockers, n (%)	45 (95.7)	29 (100)	16 (88.9)
ACE inhibitors/ARB, n (%)	16 (34)	11 (37.9)	5 (27.8)
Loop diuretics, n (%)	32 (68.1)	23 (79.3)	13 (72.2)
Aldosterone antagonists, n (%)	16 (34)	11 (37.9)	5 (27.8)
Statins, n (%)	31 (66)	19 (65.5)	12 (66.7)

Significance of differences in the subgroups of male and female patients: *, p<0.05; **, p<0.01.
The data are presented as M ±σ and the median, distribution of the 1st and 3rd quartiles. HCM, hypertrophic cardiomyopathy;
BMI, body mass index; DM, diabetes mellitus; AF, atrial fibrillation; CVA, acute cerebrovascular accident;
SCD, sudden cardiac death; NT-pro-BNP, N-terminal pro-brain natriuretic peptide;
ACE inhibitors/ARB, inhibitors of angiotensin-converting enzyme/angiotensin II receptor blockers.

Figure 1. Study design

Diagnostic method	Initial examination	Surgery	Dynamic monitoring		
			Inpatient stage: 7 days after surgery	Outpatient stage	
				Visit 1: 6 months	Visit 2: 12 months
Clinical examination	+		+	+	+
Echocardiography	+		+	+	+
Cardiac magnetic resonance imaging	+		+		
Biomarkers	+				
Histological study of myocardial biopsy material		+			

linked immunosorbent assay (ELISA) on a BioRad 690 microplate reader.

The levels of circulating biomarkers were also evaluated in the control group of apparently healthy blood donors (mean age 51.5±5 years old) for comparison purposes.

Intraoperative myocardial biopsy material was fixed in 10% neutral buffered formalin. Morphometric analysis of the preparations with Van Gieson elastic staining (Masson's elastic trichrome) was used to measure percentage of fibrosis in myocardial biopsy material.

Results of statistical analysis of the data with approximately normal distribution are presented as the arithmetic mean (M), standard deviation (σ), and the number of signs per group (n). Discrete variables or continuous quantitative variables with abnormal distribution were presented using the median with interquartile range. The significance level was set at $p<0.05$. Correlations between pairs of quantitative variables were estimated using the nonparametric Spearman's rank correlation coefficient. To identify the independent effect on the quantitative variables of qualitative factors, a one-way analysis of variance (ANOVA) was used.

Results

Analysis of findings showed that female patients suffering from HCM were older ($p<0.05$), had hypertension more often ($p=0.05$), and smoked more rarely ($\chi^2=9,57$; $p=0.002$) (Table 1). The subgroups also differed by the severity of clinical manifestations of the disease. For example, male patients had syncope more often ($p=0.05$). They also were at higher risk of SCD ($p=0.028$). Analysis of the echocardiographic parameters and MRI findings revealed that male patients had a higher index of LV myocardial mass than female patients (443 [338; 514] g/m² and 337 [251; 394] g/m², respectively).

Interstitial fibrosis with the mean area 13.9±6.9% was identified histologically in intraoperative myocardial biopsy material, together with common changes typical of HCM, such as cardiomyocyte hypertrophy, polyploidy, damaged myofibril architectonics, and thickened intramural coronary artery walls. MRI of the heart identified

Table 2. Instrumental examination

Parameter	Baseline	7 days	6 months	12 months
		After surgery		
Echocardiography				
LA, mm	46±6	44±5	46±3	46±6
IVS, mm	22±4	14±3	14±3	16±3
LVPW, mm	14±4	14±3	12±4	13±4
RVT	0.808±0.169	-	-	-
EDD, mm	46±6	48±4	47±13	49±5
ESD, mm	26±5	30±4	28±10	26±1
EF, %	69±8	67±7	65±5	58±5
LVMMI, g/m²	255±94	-	-	-
LVOT, dPmax	88±30	17±7	11±6	12±8
MR, degree	2 (0; 3)	0 (0; 2)	1 (0; 3)	1 (0; 2)
Ve/Va	1.0±0.4	-	1.1±0.4	1.0±0.4
DT, ms	260±87	-	240±24	191±40
RV, mm	29±4	26±2	28±9	27±3
Cardiac magnetic resonance imaging				
IVS, mm	24±4	15±5	-	-
LVPW, mm	13±3	12±2	-	-
EDV, mL	129±30	123±24	-	-
ESV, mL	36±15	44±16	-	-
EF, %	72±8	64±8	-	-
SO, mL	92±24	79±17	-	-
RV, mm	31±6	29±5	-	-
RV, mm	43±6	41±7	-	-
SAM	(+) 100%	(-) 100%	-	-
LGE, % of patients	(+) 100%	(+) 100%	-	-
% of fibrosis of LV mass	8.7±3.3%	-	-	-

Data are presented as M±σ and the median, distribution of the 1st and 3rd quartiles. LA, left atrium; IVS, interventricular septum; LVPW, left ventricular posterior wall; RWT, relative wall thickness of left ventricle; EDD, end-diastolic dimension; ESD, end-systolic dimension; EDV, end-diastolic volume; ESV, end-systolic volume; EF, ejection fraction; LVOT, left ventricular outflow tract; dPmax, maximum transvalvular pressure gradient; MR, mitral regurgitation; DT, deceleration time; RV, right ventricle; RA, right atrium; SAM, systolic anterior motion of the mitral valve; LGE, late gadolinium enhancement.

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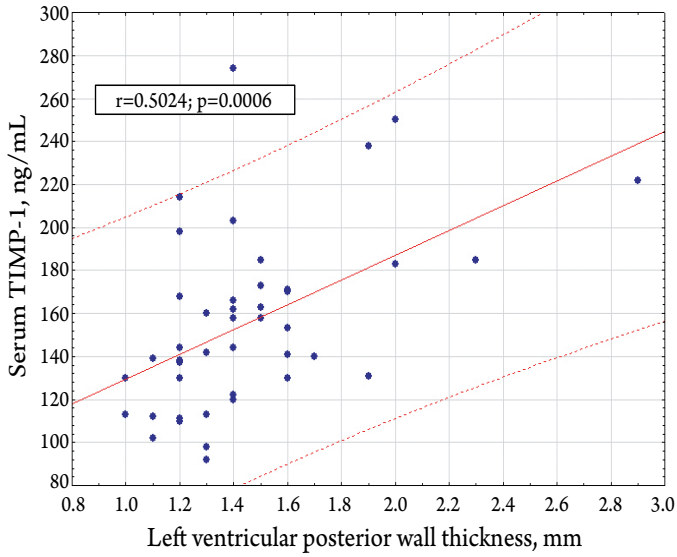
the signs of delayed enhancement, varying from 4% to 15% depending on LV myocardial mass, in all patients included in the study. According to the analysis of post-enhancement, MRI sequences showed that the mean percentage of fibrotic changes in the myocardium was 8.7±3.3% (Table 2).

The test on serum circulating markers of fibrosis in patients with the obstructive form of HCM revealed an increase in collagen type I and III metabolites, mainly due to the increase in markers of collagen type I synthesis (Table 3). Increased levels of CITP indicated disturbances of collagen degradation in patients with HCM, which correlated with the increase in percentage of fibrotic changes of the myocardium according to histological examination (r=0.356; p=0.028). Although there were no differences in the serum levels of TIMP-1 (factor regulating the degradation of collagen) in patients with HCM versus subjects from the control group, a direct correlation between the production of TIMP-1 and LV wall thickness was established (Figure 2). Interestingly, patients with HCM had significantly elevated levels of MMP-9, which are commonly thought to result from inflammatory cells. This is supported by the data showing an increase in the levels of circulating TGF-β1 and sST2. The increased serum levels of galectin-3 also show the relationship between the processes of inflammation and fibrosis.

As for sex differences, it should be noted that among patients with HCM, male patients have higher serum levels of TIMP-1 and sST2 than female patients: 173 (141; 222) ng/mL versus 141 (116; 164) ng/mL; p=0.004 and 26.5 (18.7; 32) ng/mL versus 18 (14.4; 22.1) ng/mL; p=0.0008, respectively, which can be considered as an additional risk factor (RF) for the development of fibrotic changes in male patients with HCM.

There is no association of common RFs and, primarily, hypertension with the severity of fibrotic changes in the myocardium and the levels of circulating markers of fibrosis. This may be due to the modifying effect of drug therapy administered to patients with HCM. For example, patients receiving aldosterone antagonists had higher serum concentrations of TGF-β1 (24.6 [20.8; 39.9] ng/mL and 18 [11.9; 22.8] ng/mL, respectively; p=0.0007) and sST2 (22.6±7.3 ng/mL and 17.6±7.3 ng/mL, respectively; p=0.001) than patients who did not receive such therapy. Probably, aldosterone antagonists were administered to patients with more severe manifestations of heart failure (HF) who had higher levels of TGF-β1 and sST2. This is supported by the direct association of NT-proBNP levels with intraventricular septum thickness (r=0.390; p=0.009) and an increase

Figure 2. Correlation between left ventricular wall thickness and serum levels of TIMP1



TIMP-1, ng/mL=72.1812+57.4273 x x 0.95 Pred. Int.

Table 3. Serum levels of circulating biomarkers in patients with hypertrophic cardiomyopathy and control subjects

Parameter	Control group, n=20	Patients with HCM, n=47
Galectin-3, ng/mL	6.07±1.43	8.26±2.06**
MMP-2, ng/mL	312±95	255±81*
MMP-9, ng/mL	283 (249; 509)	1153 (683; 1.569)**
TIMP-1, ng/mL	146±38	161±51
MMP-9/ TIMP-1 ratio	2.8 (1.8; 4.6)	7.6 (4.3; 10.7)**
CITP, ng/mL	0.311 (0.269; 0.415)	0.467* (0.273; 0.677)
PICP, ng/mL	28.5 (17; 59)	69 (33; 199)*
PIIINP, ng/mL	11.0 (8.4; 12.7)	12.3 (8.6; 30.1)†
PICP/PIIINP ratio	3.9 (2.2; 5.4)	4.6 (2.9; 8.7)
TGF-β1, mg/mL	13.1 (12.0; 18.6)	21.0 (12.8; 25.0)*
sST2, pg/mL	15.4 (11.8; 18.5)	19.6 (15.7; 26.3)*

Significance of differences versus the control: †, p<0.05; *, p<0.01; **, p<0.001. Data are presented as M ±σ and the median, distribution of the 1st and 3rd quartiles. HCM, hypertrophic cardiomyopathy; MMP, matrix metalloproteinase; TIMP-1, tissue inhibitor of matrix metalloproteinases type 1; CITP, C-terminal telopeptide of type-1 collagen; PICP, C-terminal propeptide of type-1 collagen; PIIINP, N-terminal propeptide of procollagen type III; TGF-β1, transforming growth factor-beta 1; sST2, soluble ST2 receptor 4 for interleukin 1 (IL1 R4).

in the left atrial diameter (r=0.314; p<0.05). Such a paradoxical drug effect is seen in the analysis of the associations with statin treatment: patients treated with statins were at lower risk of SCD (2.6% [2.2; 3.8]) than patients who did not receive such therapy (3.75% [2.65; 5.95]); p<0.05. Perhaps it can be explained by the epidemiology of SCD in patients with HCM, the risk of which is higher in patients less than 30 years old. At the

same time, common RFs which are effectively corrected by statins are more pronounced at an older age.

According to the echocardiographic examinations, the maximum LVOT pressure gradient before surgical treatment was 88 (55; 192) mmHg; the thickness of the intraventricular septum was 22 mm (16; 32) (Table 2). After myomectomy, a significant reduction in the LVOT gradient was observed in all patients (p=0.0002). However, the left atrial dimension, which tended to decrease in the early postoperative period, returned to the baseline values by the 6th month of follow-up.

Discussion

Several large-scale studies, which analyzed the data of patients with HCM, as well as our study, have noted that female patients were older, had more severe clinical manifestations and echocardiographic signs of diastolic dysfunction, and required more intensive monitoring and earlier consideration of surgical tactics [3, 4]. Violation of myocardial relaxation in patients with HCM can be associated both with mutations of cardiomyocyte contractile proteins and the development of hypertrophy and with the increase in fibrosis. There are no sex differences in the functional properties of the myofibrils and their sensitivity to calcium. Yet the specific nature of phosphorylation of sarcomeric proteins and the composition of titin isoforms were identified in female patients. These data and a higher percentage of fibrotic changes in the myocardium, which has been shown by Nijenkamp et al., can explain the phenomenon of sex differences in HCM [5]. Given a limited number of subjects, we detected only a trend toward an increasing percentage of fibrotic changes in the myocardium in female patients with HCM: 13.1% (8.0; 18.8) versus 11.1% (9.6; 15.5). It should be noted that hypertension, which was more common in female patients in our study, can also be an additional cause of fibrotic changes in the myocardium in patients with HCM.

The normal ventricular function requires intact myocardial architectonics. The disbalance between the synthesis and degradation of proteins of the extracellular matrix results in functional disorders and primarily in an increase in myocardial rigidity. Therefore, the development of myocardial fibrosis in cardiovascular disease (CVD) is associated with systolic and diastolic dysfunction, arrhythmias, and SCD. Moreover, in hemodynamic stress, perivascular fibrosis can disturb the myocardial perfusion. In obstructive HCM, interstitial and perivascular fibrosis can be triggered by pressure overload associated with LVOT obstruction, volume overload due to mitral insufficiency, and microvascular myocardial ischemia. However, this study showed that the elimination of LVOT obstruction has no significant influence on the long-term prognosis of structural changes in the myocardium. Early diagnosis of fibrotic changes in the myocardium in HCM thus seems to be relevant [6].

Histological examination of the myocardial biopsy material is traditionally considered the gold standard in the diagnosis of fibrotic changes. However, a limited amount of the material to be examined and the focal nature of the process do not always result in a reliable reflection of the general severity of fibrotic changes in the myocardium. Fibrosis mosaicism can be shown by histological examination of intraoperative myocardial biopsy material taken from one patient, in different parts of one segment (Figure 3).

The echocardiographic examination also allows identifying fibrotic changes through the analysis of a range of the pixel distribution density range, which is closely correlated with the collagen volume fraction. However, the diagnostic value of this approach needs to be clarified. The severity of fibrotic changes can be indirectly judged by the analysis of LV diastolic function and an increase in the left atrial volume.

Contrast-enhanced cardiac MRI provides additional means for analysis of the severity of fibrotic changes. For example, a quantitative assessment of extracellular volume helps to describe diffuse structural changes of the myocardium. Correlation between LV hypertrophy, according to the estimation of myocardial mass, its systolic/diastolic function, and area of delayed enhancement, was established. However, this study did not reveal any associations of delayed enhancement with the indicators of myocardial damage (levels of troponin I), heart failure (natriuretic peptide), markers of collagen synthesis and degradation (PICP, CITP, MMP-1, TIMP-1), or with patient's age, the severity of LV hypertrophy, and left atrial dimension.

Cardiomyocytes, vascular wall cells, and inflammatory cells may contribute to the development of fibrosis not only through the secretion of profibrogenic factors but also via the production of endogenous proteases involved in the metabolism of the extracellular matrix. The latter disrupts the relationship between the myocardial stroma and contractile elements, resulting in its dysfunction. High serum levels of MMP-9 detected in this study reflect the intensity of extracellular matrix renewal, which determines the progression of myocardial hypertrophy and fibrotic changes associated with the development of cardiovascular complications [7].

TGF-β1 is currently recognized as the main paracrine regulator of the formation of connective tissue, due to which the main effects of angiotensin II are realized at the

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cellular level. This is a unique growth factor due to the pleiotropic nature of its activity. It stimulates the cells of mesenchymal origin (fibroblasts, mast cells, adipocytes) and inhibits the cells of epithelial (endothelium) and neuroectodermal nature. We detected the increased levels of TGF-β1 in the examined patients with HCM, which is consistent with the previous study, in which patients with higher – functional capacity congestive heart failure, higher levels of the natriuretic peptide, and more frequent rehospitalizations had elevated levels of TGF-β1 [8]. Thus, elevated levels of TGF-β1 can predict adverse events in patients with HCM.

Circulating galectin-3, which reflects the association of inflammation, fibrosis, and reparation, has been successfully used in recent years to assess the severity of structural changes of the myocardium. The recent meta-analysis confirmed that serum levels of galectin-3 could be used as an independent predictor of mortality and rehospitalizations in patients with HF [9]. In our study, levels of galectin-3 were significantly elevated in both male and female patients. However, no direct correlation between the severity of fibrotic changes and indicators of diastolic dysfunction of the myocardium was observed, which can be possibly explained by the limited size of the sample.

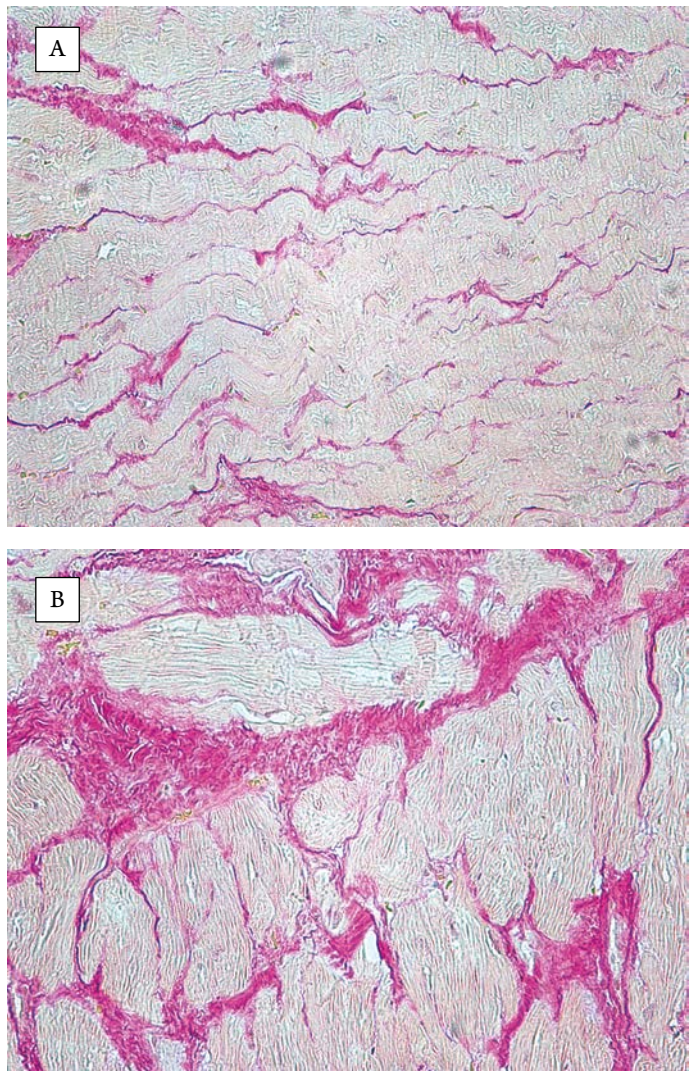
The interleukin (IL) – 33/ST2L system, having a cardioprotective effect, is activated by biomechanical stress. The soluble isoform of sST2 is highly affinitive to IL-33. It competes with a transmembrane isoform of ST2L for receptor binding, resulting in the interruption of the interaction between IL-33 and its ligand, which is accompanied by a loss of the cardioprotective effect. Therefore, the elevated levels of sST2 were considered to be a prognostic marker of inflammation and CVD [10]. According to the published data, sST2>35 pg/mL is associated with an adverse prognosis in patients with HF. However, in our study, sST2 levels did not exceed 26 pg/mL in any of the patients, which, given their age and drug treatment, indicated a relatively favorable course of the disease.

The predictors of SCD include delayed enhancement, an MRI marker of fibrotic changes in the myocardium, and well-known key RFs [11]. The increase in the percentage of late enhancement of ≥15% of the myocardial mass was shown to be associated with a two-fold increase in the risk of SCD [12]. However, as of yet there are no clear recommendations on how to use this criterion when deciding on the management of patients with HCM [13].

Conclusion

The importance of fibrotic changes in the myocardium should be emphasized not only for predicting the risk of SCD, which in this study was closely related with the percentage of fibrosis (r=0.337; p=0.03), but also because of the need for treatment modification due to reduced efficacy of reverse remodeling of the left cardiac chambers in the long term after septal myectomy. The high levels of circulating relevant markers of fibrosis and the fact that cardiac fibrosis is primarily a humoral-dependent event require the administration of renin-angiotensin-aldosterone system (RAAS) blockers in patients with HCM after septal myectomy.

Figure 3. Sample of fibrosis mosaicism in different sections (A and B) of one segment in one patient. Elastic Van Gieson stain x200



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