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MULTIMARKER APPROACH FOR ASSESSING EFFICIENCY OF CARDIAC RESYNCHRONIZATION THERAPY IN PATIENTS WITH SINUS RHYTHM

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Purpose. To design a mathematical model, that can predict a positive response to cardiac resynchronization therapy (CRT) in patients with congestive heart failure (CHF) and sinus rhythm, according to complex analysis of neurohumoral and immune activation biomarkers, fibrosis, renal dysfunction, echocardiography.

Methods. Parameters of echocardiography, plasma levels of NT-proBNP, interleukins-1β, 6, 10, tumor necrosis factor α, C-reactive protein (CRP), matrix metalloproteinase-9 (MMP-9), tissue inhibitors of metalloproteinase 1 and 4, cystatin C (CYSTATIN) were studied in 40 CHF patients with sinus rhythm (65% coronary artery disease patients, 75% males, mean age 54.8±10.6 years old) during the period of maximum decrease of left ventricular end-systolic volume (LVESV) (mean duration 27.5 [11.1; 46.3] months). Responders (decrease in LVESV ≥15%) and non-responders (decrease in LVESV <15%) were identified.

Results. The number of responders was 26 (65%). The initial set of variables included: age, left ventricular ejection fraction (EF), pulmonary artery systolic pressure, right ventricle size and NT-proBNP, CRP, MMP-9, CYSTATIN. According to logistic regression analysis, a prediction model of positive CRT response was created. The specificity of the model was 92.9%, sensitivity - 83.3%, AUC=0.952 ($p<0.001$).

Conclusion. The proposed model, based on the assessment of left ventricle EF and circulating biomarkers of inflammation, fibrosis, and renal function, strongly suggests a higher possibility of response to CRT.

Key words: cardiac resynchronization therapy; immune inflammation; fibrosis; renal dysfunction

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With an increasingly aging population, the prevalence of congestive heart failure (CHF) in the Russian Federation is steadily growing and amounts to more than 14 million people, which allows us to call the disease a global problem of modern cardiology [1]. CHF is a disease with a complex set of pathophysiological mechanisms, the study of which is accompanied by the improvement of treatment methods. Cardiac resynchronization therapy (CRT) has revolutionized the treatment of patients with reduced left ventricular (LV) systolic function and widened QRS complex due to improved quality and longer life expectancy, reduced hospitalization rates and mortality [2].

Currently, there is no unified approach to assess the efficacy of CRT. Along with the use of indicators of clinical response, functional criteria, laboratory markers, as well as their various combinations, the most often there used reduction of LV end-systolic volume (LVESV) by 15% or more [3]. Despite the constantly changing selection criteria for implantation of CRT devices, its efficiency is about 70% [4]. Non-responders compared to responders have a higher risk of ventricular arrhythmias, cardiovascular events, and overall mortality [5]. In this connection the ineffectiveness of CRT is a serious clinical problem, which is probably multifactorial and can be caused by suboptimal positioning of the electrodes and programming of the device, the presence of postinfarction scar, the absence of "corrected dyssynchrony", as well as the presence of concomitant diseases [6], among which renal insufficiency plays a major role [7].

Deterioration of renal function in patients with CHF occurs from 40% to 70% and is a predictor of disease progression and mortality in patients, including those receiving CRT [8]. The molecular mechanisms of CRT influence are being actively studied. The association of cardiac remodeling in connection with CRT with a decrease in the activity of immune inflammation, neurohumoral activation, and fibrosis has been established [9-11]. However, none of the studied biomarkers can predict a positive response to CRT. In this connection, the search for predictors of a favorable response to CRT is highly relevant. The modern direction of research is a multimarker approach with an assessment of various pathophysiological mechanisms of the pathogenesis of CHF.

The aim of our study was to create a mathematical model capable to predict a favorable response to CRT in patients with CHF and stable sinus rhythm based on complex analysis of biomarkers of neurohumoral and

immune activation, fibrosis, renal dysfunction, echocardiographic parameters.

MATERIAL AND METHODS

Forty patients with CHF from the "Register of performed operations of cardiac resynchronization therapy" (Certificate of state registration of the database No. 2010620077 dated February 1, 2010) (65% of ischemic, 75% men) and stable sinus rhythm aged 30 to 74 years (mean age 54.8±10.6 years) were included in the study consecutively from 2003 to 2017. Patients signed an informed consent to conduct the study, which was approved by the ethics committee. To select patients for CRT devices implantation, we used the presence of intraventricular and/or interventricular dyssynchrony according to echocardiography (EchoCG), LV ejection fraction (LVEF) less than or equal to 35%, II-IV functional class of CHF, the width of QRS complex on ECG more than 120 ms.

The criteria for intraventricular dyssynchrony diagnosis in M-mode was a time delay between peaks of LV posterior wall contraction amplitude and interventricular septum over 130 ms. To diagnose intraventricular dyssynchrony, pulsed-wave Doppler in the LV outflow tract was used. Intraventricular dyssynchrony was indicated by prolongation of the pre-ejection period from left ventricle more than 140 ms, interventricular dyssynchrony - by prolongation of interventricular mechanical delay time more than 40 ms. Intraventricular dyssynchrony was determined by tissue Doppler imaging by interval difference between basal segments of LV lateral wall and interventricular septum more than 60 ms. The study was conducted at baseline, 1, 3, 6 months and every 6 months after the implantation of CRT devices. If necessary, the parameters of the CRT device were optimized. The period of the best response to CRT was estimated retrospectively according to the maximal decrease of LVESV and was 27.5 [11.1; 46.3] months. Heart failure functional class (FC) was determined based on the result of the 6-minute walk test and clinical criteria according to the New York Classification (NYHA). EchoCG was performed using a stationary Philips IE-33 ultrasound device (USA). LV end-diastolic volume (LVEDV) and LVESV, pulmonary artery systolic pressure (PASP), left atrial (LA) size and right atrial (RA) volume and right ventricular (RV) size were calculated. LVEF was assessed by the Simpson method. Plasma levels of the N-terminal fragment of natriuretic peptide (NT-proBNP), interleukins (IL)-1b, IL-6, IL-10, TNF-α, matrix metalloproteinase 9 (MMP-9) and tissue inhibitors of metalloproteinases (TIMP-1 and TIMP-4) MMP-9 were studied by solid-phase chemiluminescence enzyme immunoassay (sandwich method) on IMMULITE 1000 analyzer (Siemens Diagnostics, USA). MMP-9/TIMP-1 and MMP-9/TIMP-4 coefficients were calculated. High-sensitivity C-reactive protein (CRP) in blood serum was determined by an immunoturbidimetric method using analytical kits C-REACTIVE PROTEIN hs (BioSystems, Spain) on a Clima MC-15 analyzer (Spain). Quantitative determination of cystatin C in blood serum was performed by the sandwich method using analytical kits Human Cystatin C Elisa (BioVendor, Czech Republic). Optical density was measured using a StatFax 4200 reader.

Table 1.

Clinical characteristics of groups with different response to CRT

	I group responders (n=26)	II group non-responders (n=14)	p
Time for best response, month	31.0[22.0;50.0]	12.0[5.0;26.7]	0.005
Mean age, years	58.0±7.4	50.4±12.8	0.022
Men, n (%)	16 (69.6)	14 (82.4)	0.356
CAD, n (%)	16 (69.6)	10 (58.8)	0.481
PMI, n (%)	6 (26.1)	7 (41.2)	0.502
CABG, n (%)	3 (13.0)	0	0.124
PCI, n (%)	4 (17.4)	5 (29.4)	0.208
II FC HF (NYHA), n (%)	13 (56.6)	8 (47.1)	0.144
III FC HF (NYHA), n (%)	7 (30.4)	6 (35.3)	
IV FC HF (NYHA), n (%)	3 (13.0)	3 (17.6)	
Hypertension, n (%)	20 (87.0)	9 (52.9)	0.017
PAF	4 (17.4)	5 (29.4)	0.345
DM, n (%)	2 (8.7)	2 (11.8)	0.480
Obesity, n (%)	13 (56.5)	9 (52.9)	0.987
BMI, kg/m^2	30.7±5.5	29.3±6.2	0.492
The mean QRS duration, ms	174.7±26.3	154.7±20.1	0.011
CLBBB, n (%)	20 (87.0)	10 (58.8)	0.042
Antiarrhythmic drug use, n (%)	3 (13.0)	9 (52.9)	0.021
MRA, n (%)	20 (87.0)	15 (88.2)	0.904
Diuretics, n (%)	19 (82.6)	16 (94.1)	0.277
Calcium channel blockers, n (%)	7 (16.7)	0	0.070
BB, n (%)	20 (87.0)	15 (88.2)	0.904
Digoxin, n (%)	4 (17.4)	1 (5.9)	0.277
ACEI, n (%)	16 (69.6)	14 (82.4)	0.356
ARB, n (%)	6 (26.1)	2 (11.8)	0.263
Statins, n (%)	19 (82.6)	5 (29.4)	0.001

Notes: CAD - coronary artery disease; PMI - previous myocardial infarction; CABG - coronary artery bypass grafting; PCI - percutaneous coronary intervention; FC HF (NYHA) - functional class of congestive heart failure according to the New York Heart Association classification; PAF - paroxysmal atrial fibrillation; DM - diabetes mellitus; BMI - body mass index; CLBBB - complete left bundle branch block; MRA - mineralocorticoid receptor antagonists; BB - beta-blockers; ACEI - angiotensin converting enzyme inhibitors; ARB - angiotensin II receptor blockers.

Statistical analysis was performed using the SPSS 21 software package (SPSS Inc., Chicago, IL, USA). The distribution normality was assessed using the Kolmogorov-Smirnov method. If the distribution is normal, the results are presented as M±SD, where M is the mean value, SD is the standard deviation; if the distribution is not normal, the results are presented as the median and interquartile range (Me [25; 75]). The chi-square test was used to analyze qualitative data in unrelated groups. To compare quantitative indicators in unrelated groups with their normal distribution, the Student's t-test was used, with a distribution other than normal - the Mann-Whitney test, in related groups - paired Student's t-test or Wilcoxon's test. The mathematical model was constructed using logistic regression. ROC analysis was used to find the optimal diagnostic point of separation (threshold value) of the indicators and assess the diagnostic significance of the model. Differences were considered significant at $p<0.05$.

RESULTS

According to the dynamics of LVESV in connection with CRT, 2 groups of patients were distinguished: group 1 (n=26; 65%) - responders (decrease in LVESV >15%); group 2 (n=14; 35%) - non-responders (decrease in LVESV <15%). Clinical characteristics of the study groups are presented in Table 1. Patients of group 2 were younger, they are less likely to suffer from arterial hypertension and took antiarrhythmic drugs and statins. In group 2, a shorter period of better response to CRT was revealed, lower incidence of complete left bundle branch block (CLBBB) and the duration of QRS complex was noted.

Table 2.

Dynamics of echocardiographic parameters and exercise tolerance

		I group responders (n=26)	II group non-responders (n=14)	P between groups
6MWT, m	initially	292.6±100.8	302.7±128.8	0.797
	follow-up	379.5±83.8	339.7±75.0	0.145
p in group		<0.001	0.450	
LA, mm	initially	46.8±5.1	49.6±5.7	0.123
	follow-up	43.3±7.5	48.4±5.3	0.016
p in group		0.027	0.251	
RA, ml	initially	61.6±19.0	68.6±20.4	0.292
	follow-up	51.7±17.5	78.1±15.9	<0.001
p in group		0.018	0.198	
RV, mm	initially	28.0±3.2	31.3±3.8	0.007
	follow-up	26.2±17.5	30.8±3.6	<0.001
p in group		0.014	0.661	
LVESD, mm	initially	56.9±6.9	61.3±9.3	0.276
	follow-up	43.2±9.1	56.9±6.3	0.001
p in group		0.010	0.419	
LVEDD, mm	initially	65.4±6.0	68.8±8.1	0.158
	follow-up	56.8±7.8	67.9±7.8	0.001
p in group		<0.001	0.573	
LVESV, ml	initially	150.8±39.8	178.4±55.4	0.091
	follow-up	82.8±39.1	168.6±51.7	<0.001
p in group		<0.001	0.010	
LVEDV, ml	initially	220.7±46.5	249.7±69.1	0.147
	follow-up	150.2±49.8	242.2±65.2	<0.001
p in group		<0.001	0.047	
EF, %	initially	32.3±5.1	29.0±4.6	0.042
	follow-up	46.9±8.6	30.9±5.0	<0.001
p in group		<0.001	0.022	
PASP, mmHg	initially	39.5±8.8	50.1±11.2	0.011
	follow-up	29.9±13.1	46.9±11.6	0.001
p in group		0.193	0.036	

Notes: 6MWT - 6-minute walk test; LA - left atrium; RA - right atrium; RV - right ventricle; LVESD - left ventricular end-systolic dimension; LVEDD - LV end-diastolic dimension; LVESV - LV end-systolic volume; LVEDV - LV end-diastolic volume; LVEF- LV ejection fraction; PASP - pulmonary artery systolic pressure.

The dynamics of echocardiographic parameters and exercise tolerance according to the 6-minute walk test are presented in Table 2. While there were no dynamics of exercise tolerance according to the 6-minute walk test in group 2, there was a highly significant increase in group 1.

According to EchoCG, patients in group 2 initially and in dynamics had larger RV sizes and PASP, initially a tendency towards greater LVESV and significantly lower LVEF. In dynamics in connection with CRT, in group 2 there was a significant decrease only in LVESV, LVEDV, PASP and an increase in LVEF.

In group 1, there was a significant decrease in LA, RA, RV, LV end-systolic dimension (LVESD), LV end-diastolic dimension (LVEDD), LVESV, LVEDV, and increase in LVEF. The degree of RA change was significantly opposite in the groups. The degree of decrease in LVESD, LVEDD, LVESV, LVEDV and increase in LVEF were more significant in group 1.

The results of the analysis of the dynamics of biomarkers of immune inflammation, neurohumoral activation and fibrosis, as well as cystatin C in groups with different responses to CRT are presented in Table 3. Initially, group 2 patients had significantly higher levels of CRP, cystatin C, MMP-9, and a tendency to higher values of NT-proBNP.

Analysis of biomarkers of immune inflammation did not reveal significant dynamics in group 2. Only a tendency to decrease in TNF-α concentration was noted. A significant decrease in the levels of IL-1β, IL-6, IL-10, TNF-α was detected in group

1 in connection with CRT. No differences, dynamics and degree of change in galectin-3 were revealed in the groups.

In the dynamics, there was a tendency for a decrease in MMP-9 levels in group 2, while there were no significant changes in MMP-9 concentration in group 1. The degree of change in MMP-9 was significantly opposite in the groups (37.9[-48.3;106.1] ng/mL in group 1 vs -73.2[-108.9;8.6] ng/mL in group 2; p=0.017). MMP-9 concentration was significantly higher in group 1 in connection with CRT. There were no differences between the groups in the dynamics of TIMP-1 and TIMP-4 levels. While there were no dynamics of MMP-9/TIMP-1 and MMP-9/TIMP-4 ratios in group 2, there was a significant increase in the MMP-9/TIMP-1 ratio in group 1, as well as a tendency to higher MMP-9/TIMP-4 in connection with CRT.

ROC analysis was used to investigate the prognostic significance of all biomarkers studied. For optimal recognition of patients with a likely favorable response to CRT, threshold values of the following parameters were established: NT-proBNP (1432.0 pg/mL, sensitivity 86.7%, specificity 63.6%, AUC=0.745, p=0.012), CRP (4.29 mg/mL, sensitivity 80.0%, specificity 77.3%, AUC=0.753, p=0.010), MMP-9 (155.75 ng/mL, sensitivity 78.6%, specificity 61.1%, AUC=0.706, p=0.048), cystatin C (0.395 mg/L, sensitivity 85.7%, specificity 65%, AUC=0.759, p=0.011).

When conducting multivariate analysis (binary logistic regression), the initial set of variables included signs that were significantly different or tended to differ in the studied groups of patients, such as age, RV size, PASP, LVEF, MMP-9, CRP, cystatin C, NT-proBNP.

As a result of the analysis, a model with four variables was created. The technical result is expressed by the formula for calculating the value of the function F: F = 3.231 + 0.344 x EF - 3.479 x CYSTATIN - 0.039 x MMP9 - 0.638 x CRP, where EF is the LVEF in %; CYSTATIN is the cystatin C level in mg/l; MMP9 - the level of matrix metalloproteinase 9 in ng/l; CRP is the level of C-reactive protein in ng/L.

The prediction of the response to CRT is carried out according to the formula: P=1/(1e (-F)), where P is the probability that the event of interest will occur (develop-

Table 3.

Biomarkers of immune and neurohumoral activation, fibrosis, cystatin C in groups with different response to CRT

		I group responders (n=26)	II group non-responders (n=14)	P between groups
IL-1β, pg/mL	initially	3.8[2.9;4.4]	3.9[3.2;4.4]	0.996
	follow-up	2.7[2.4;3.2]	3.7[3.2;5.3]	0.028
p in group		0.022	0.598	
IL-6, pg/mL	initially	2.6[2.4;3.3]	3.3[2.8;5.3]	0.108
	follow-up	2.3[1.7;2.5]	3.7[2.1;8.0]	0.002
p in group		0.010	0.388	
IL-10, pg/mL	initially	2.4[1.6;5.0]	3.1[2.4;4.8]	0.408
	follow-up	1.9[1.6;2.2]	3.7[2.1;4.7]	0.004
p in group		0.045	0.814	
TNF-α, pg/mL	initially	8.3[6.4;10.1]	8.6[6.7;11.2]	0.527
	follow-up	5.4[4.1;7.9]	5.6[4.5;9.2]	0.501
p in group		0.021	0.066	
CRP, mg/mL	initially	2.4[0.9;4.3]	7.2[4.5;10.1]	0.010
	follow-up	1.4[0.8;3.6]	6.2[3.4;10.1]	0.002
p in group		0.514	0.670	
Cystatin C, mg/L	initially	0.2[0.2;0.4]	0.9[0.4;1.8]	0.011
	follow-up	0.5[0.2;1.8]	0.3[0.2;1.9]	0.553
p in group		0.212	0.731	
NT-proBNP, pg/mL	initially	1044.5[673.5;2786.0]	2794.5[1499.3;5230.3]	0.094
	follow-up	518.0 [174.5;1894.5]	2232.5[1140.8;4155.0]	0.155
p in group		0.335	0.946	
MMP-9, ng/mL	initially	144.4[110.4;203.7]	190.2[157.2;255.2]	0.038
	follow-up	218.2[145.1;264.6]	130.6[101.8;236.3]	0.022
p in group		0.119	0.078	
TIMP-1, ng/mL	initially	297.4[201.8;471.5]	409.4[272.3;473.4]	0.649
	follow-up	240.9[163.3;358.2]	354.5[205.0;441.5]	0.107
p in group		0.107	0.649	
TIMP-4, ng/mL	initially	2203.0[1461.1;2686.8]	2138.6[1665.6;2082.8]	0.900
	follow-up	2067.1[1570.7;2495.3]	2301.9[1860.4;2715.1]	0.410
p in group		0.624	0.736	
MMP-9/ TIMP-1, n	initially	0.5[0.3;0.8]	0.5[0.4;0.7]	0.774
	follow-up	0.7[0.5;1.5]	0.5[0.2;0.7]	0.014
p in group		0.045	0.651	
MMP-9/ TIMP-4, n	initially	0.07[0.05;0.1]	0.09[0.07;0.1]	0.336
	follow-up	0.1[0.08;0.1]	0.07[0.03;0.1]	0.065
p in group		0.232	0.480	

Notes: IL - interleukin; TNF-α - tumor necrosis factor α; CRP - C-reactive protein; NT-proBNP - N-terminal fragment of the prohormone brain-type natriuretic peptide; MMP-9 - matrix metalloproteinase 9; TIMP-1 & TIMP-4 - tissue inhibitors of matrix metalloproteinase 1 and 4.

ment of a response to CRT); e is a mathematical constant equal to 2.718; F is the value of F function. If the P-value is less than 0.696, then the non-responder group is determined, and if the P-value is greater than or equal to 0.696, then the responder group is determined and the response to CRT is predicted. The specificity of this model was 92.9%, and sensitivity was 83.3%. The area under the ROC curve was 0.952 ($p<0.001$), which corresponds to the excellent quality of the model (Fig. 1).

DISCUSSION

We believe that for adequate assessment of the effectiveness of CRT, it is necessary to use not a fixed time frame, but the time frame for the best response to CRT to maximize the reduction of LVESV, which makes it possible to take into account the individual adaptive capabilities of patients. We have previously shown that in several patients, during the first year of follow-up, there are no positive dynamics of LVESV. However, in later terms, these patients more often become super-responders (decrease of LVESV >30%) [12]. The results of this study again confirmed significantly longer term of the best response on CRT in the group of responders in comparison with non-responders.

According to EchoCG data, group 2 patients had an initially larger size of RV, the prognostic significance of which is discussed in the literature [13], as well as significantly higher values of PASP initially and in dynamics, were revealed. In connection with CRT, the degree of change in RA volume was the opposite in the groups: it decreased in group 1 and increased in group 2. Previously, the association of decreased RV function with increased levels of creatinine and brain natriuretic peptide has been revealed [14]. In our study, there was a tendency for higher basal NT-proBNP levels in patients of group 2. Possible mechanisms of the negative effect of enlarged right parts of the heart are the increase in stagnation, reduction of renal blood flow, with the subsequent development of renal dysfunction. In connection with CRT in patients of group 1 echocardiographic parameters improved not only in the left but also in the right parts of the heart, confirming the literature data on the ability of CRT to cause favorable RV remodeling [15].

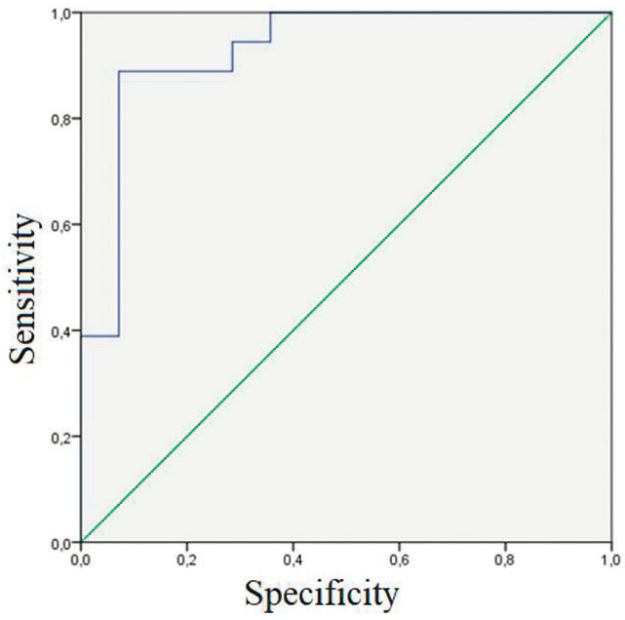

Fig. 1. ROC-curve of logistic regression (AUC=0.952, p<0.001).

It is known that activation of immune inflammation mediated by IL-1β, IL-6, IL-10, CRP, TNF-α plays a central role in the development of heart failure [16]. A close association of cytokine levels with the severity of clinical manifestations of CHF has been revealed [17]. The association of the effectiveness of CRT with a decrease in immune activation has been established [9], which is confirmed by the results of our study - a significant decrease in IL-1β, IL-6, IL-10, TNF-α was detected in the group of responders. We did not reveal any significant dynamics of CRP in the studied groups. However, its significantly higher level in the non-responders group and inclusion in a model capable of predicting response to CRT indicates an important role of CRP as a marker of immune activation, as well as the importance of immune inflammation in the effectiveness of CRT.

It was found that inflammatory mediators, through the activation of cell signaling pathways such as TGF-β/Smad and Notch [18], contribute to the activation of matrix metalloproteinases (MMPs) that play a key role in extracellular matrix (ECM) reconstruction. ECM is a dynamic environment. Being an important adaptive factor at the initial stages of the disease, the reorganization of ECM becomes a factor in pathogenesis during the progression of CHF. The activity of MMPs can be blocked by tissue inhibitors of MMPs - TIMPs. The imbalance between MMPs and TIMPs, assessed by the ratio of MMPs/TIMPs, leads to uncontrolled activation of MMPs, imbalance between ECM synthesis and degradation, fibrogenesis, cardiac remodeling, and progression of CHF. The true function of MMPs and TIMPs is still not well understood. There is little information about the specific types of MMPs and TIMPs involved in the processes of tissue remodeling in CHF, and in some cases, it is contradictory, which may be due to different expression patterns of hormones, growth factors, inflammatory mediators, and the stage of the disease.

The relationship between the increase in the concentration of MMP-9, TIMP-1 [19, 20], and the severity of CHF has been established. The available information regarding their predictive usefulness in CHF and CRT is controversial [21]. In some studies, there was no change in the level of MMP-9, TIMP-1 in connection with CRT [22], while others showed a significant decrease [23]. In the study by M. Szulik et al. significant decrease in the expression of MMP-9 in connection with CRT was observed only in 67% of patients with ischemic cardiomyopathy and was associated with a lower baseline concentration of CRP [24]. In most studies, no correlations between the levels of MMP-9, TIMP-1, and LV geometry parameters were found, and therefore the exact relationship between collagen turnover and response to CRT remains unclear. We did not find in the literature data on the effect of CRT on the TIMP-4 level.

According to our study, there were no significant dynamics in the level of MMP-9, TIMP-1, TIMP-4 in the studied groups. However, the degree of MMP-9 change in

the groups was the opposite - it increased in responders and decreased in non-responders. In connection with CRT, the group of responders tended to have a higher MMP-9/TIMP-4 ratio and a significantly higher MMP-9/TIMP-1 ratio. Since this pattern of changes in fibrosis biomarkers was detected in the group of favorable responses to CRT, it probably has a positive physiological meaning. In the study by D. D. Bonnema et al. decrease in the ratios MMP-9/TIMP-1, MMP-9/TIMP-4, and MMP-2/TIMP-4 during aging was found, which indicates a reduced ability to degrade ECM with age and contributes to the development of interstitial fibrosis [25]. MMP-9/TIMP-1 and MMP-9/TIMP-4 coefficients likely reflect the preserved ability to reconstruct ECM and the higher adaptive capacity of responders, despite their older age.

It is known that renal function is an important predictor of adverse clinical course of CHF, mortality, response to CRT [7]. A sensitive marker of early renal dysfunction is cystatin C, the biological role of which is associated with inhibition of extracellular cathepsin activity. A baseline cystatin C level above 1 mg/L was found to be associated with a fourfold increased risk of non-response to CRT, as well as an increased risk of developing significant cardiovascular events within two years [26]. Probably, the level of cystatin C is linearly related to the risk of progression of heart failure due to its revealed correlation with the level of NT-proBNP [27]. The combination of high levels of cystatin C and NT-proBNP is associated with a ninefold increase in the risk of non-response to CRT [28]. According to our study, the baseline level of cystatin C in non-responders was significantly higher than in responders, which confirms the effect of renal function on the effectiveness of CRT.

In the presented model, the combination of MMP-9, CRP and cystatin C demonstrates a close relationship between three key mechanisms of CHF pathogenesis - immune inflammation, fibrosis and renal dysfunction, which determine the severity of the disease and the response to CRT. In this model, inflammatory mediators induce the activity of MMPs. Gelatinases, which include MMP-9, through various interactions with TNF-α and TNF-β, monocytic chemoattractant proteins, growth factors, oxidative stress, affect the development and progression of renal dysfunction [29], contributing to the reconstruction of ECM, the development of renal fibrosis, blocking of the interstitial capillary beds and kidney hypoxia. There were no significant dynamics of NT-proBNP level in the studied groups, which was probably due to the small number of patients, as well as their severity. As an example of the use of the obtained mathematical model, we present 2 clinical cases.

Patient K., 64 years old, complained of dyspnea, various pains in the chest area, occurring without clear association with physical and emotional stress. Her blood pressure increased to 180/120 mm Hg within a year. She did not take hypotensive medications regularly. The deterioration of health was noted within three months. Initially, ECG revealed CLBBB (QRS-160 ms). According to echocardiography: aortic atherosclerosis, sclerosis of the aortic valve cusps with minor regurgitation; dilatation of predominantly left parts with signs of moderate mitral regurgitation; along with diffuse hypokinesis, a moderate decrease in the contractile function of the heart (LVEF-35%), LVESV-120 ml; signs of minor pulmonary hypertension, intraventricular dyssynchrony. Selective coronary angiography revealed no data for hemodynamically significant stenotic lesions of the coronary arteries. The patient was discharged with a diagnosis: Arterial hypertension, stage III, grade 3, risk of cardiovascular complications 4 (very high). CLBBB. CHF IIA FC III (NYHA). After 3 months of optimal drug therapy, complaints of shortness of breath on light physical activity, edema of the lower extremities, general weakness and fatigue, periodically varied pains in the precordial region, occurring unrelated to physical activity and relieved independently, persisted. Laboratory examination: cystatin C level - 0.21 ng/L, MMP-9 - 62.45 ng/L, CRP - 4.09 ng/L. Using available data, we calculated the F function value of 8.134 and the probability P-value of 0.999.

The obtained P-value allowed the patient to assume the development of a favorable response to CRT at the preoperative stage in addition to the generally accepted criteria. Considering clinical and anamnestic data, progression of CHF symptoms, the ineffectiveness of drug therapy, and high risk, the patient was implanted with a permanent biventricular pacemaker - Consulta Medtronic with endocardial electrodes. One week after the implantation of the CRT device, the patient noticed an improvement in her well-being. After 6 months EchoCG data showed positive dynamics in the form of volume reduction (LVESV up to 105 ml), an increase of LVEF up to 43%, a decrease of NYHA FC. After 12 months, according to EchoCG: LVESV - 85 ml, LVEF - 45%; NYHA FC II. After 18 months - LVESV - 55 ml, LVEF - 49%, in dynamics normalization of the left heart size, NYHA FC II. After 30 months - LVESV - 49 ml, LVEF - 55%, NYHA FC I. The proposed method made it possible to predict a favorable response to CRT.

Patient C., 37 years old, was observed in Tyumen Cardiology Research Center since 2005 with the diagnosis: Coronary artery disease. Previous myocardial infarction (2005). Postinfarction apical LV aneurysm. Ventricular fibrillation. Paroxysms of unstable ventricular tachycardia. CHF IIA. FC III (NYHA). Dyslipidemia. Coronary angiography was performed twice (2006, 2009): no data for stenotic lesions of the arteries were found. In 2009, the patient was implanted with a Medtronic Virtuoso DR cardioverter-defibrillator with Medtronic endocardial electrodes. In 2011 he was admitted with complaints of shortness of breath, palpitations and pressing pains in the region of the heart during exertion (going upstairs to the 2nd floor), general weakness, rapid fatigability. The arrhythmia counter of the implanted device recorded 2 episodes of unstable ventricular tachycardia (5-65 complexes). According to ECG data, CLBBB was registered (QRS - 160 ms.) According to EchoCG: increased echogenicity of the aortic walls; extensive circular cicatricial changes of LV myocardium with signs of postinfarction apical LV aneurysm; severe dilatation of the left heart with signs of moderate mitral regurgitation; LVEF - 31%; signs of intra- and interventricular dyssynchrony. Laboratory examination: cystatin C level - 0.41 ng/L, MMP-9 - 318.3 ng/L, CRP - 4.49 ng/L. Using available data, we calculated the F function value of -2.809 and probability

P-value of 0.057. The obtained P-value allowed the patient with the presence of classic criteria for implantation (NYHA FC III CHF, LVEF - 31%, CLBBB, QRS - 160 ms) to assume no responsibility to CRT. The patient was implanted with the CRT-P CONTAK RENEWAL Boston Scientific device. According to EchoCG after 6 months: LVESV - 189 ml, LVEF - 33%; NYHA FC III. After 12 months, in dynamics there was an increase in the heart cavities, LVESV - 239 ml, LVEF - 31%, NYHA FC III. Optimization of the parameters of the CRT system was carried out: AV delay - 120 ms, VV delay - 30 ms. After 18 months: LVEF - 33%, sizes of the heart cavities without significant dynamics, LVESV - 230 ml, NYHA FC III. Optimization of the parameters of the CRT system was performed: AV delay - 120 ms, VV delay - 0 ms. After 30 months: LVEF - 30%, without significant dynamics, LVESV - 232 ml, NYHA FC III. Thus, the patient was predicted to have no favorable response to CRT at the preoperative stage. However, considering available indications, the patient was implanted with a CRT-D device, but no positive effect was obtained.

STUDY LIMITATIONS

Considering our experience in the implantation of CRT devices since 2003, when there were no modern recommendations, the study included patients with QRS complex duration >120 ms. Until 2013, for referral to cardiac resynchronization, the protocol of St. Mary's Hospital (London) was used, which is based on the data of spectral tissue Doppler studies [30]. The limitation of our work is the retrospective design and the small number of patients.

CONCLUSION

Thus, our proposed method for predicting a possible response to CRT includes assessment of LVEF, as well as laboratory parameters reflecting the key mechanisms of the development and progression of CHF - immune inflammation, fibrosis, renal dysfunction. The results of the study emphasize the necessity of comprehensive examination of a patient with CHF who is a candidate for implantation of a CRT device. The use of the method suggests a response to CRT and may improve the quality of patient selection.

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