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TEN-YEAR SURVIVAL AND CLINICAL BIOCHEMICAL STATUS OF NONPROGRESSORS AND RESPONDERS TO CARDIAC RESYNCHRONIZATION THERAPY

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Aim. To estimate the 10-year survival, clinical and biochemical status of responders and non-progressors to cardiac resynchronization therapy (CRT) using biomarkers of fibrogenesis, neuro-humoral, immune, sympatho-adrenal activation.

Methods. Eighty CRT patients (mean age 58.9±10.1 years; 90% men; 72.5% with coronary artery disease) with the best CRT response timing ("best" timing), assessed by maximum decrease in left ventricle end-systolic volume (LVESV), were divided into groups: Gr.1 (n=42): non-progressors (decrease in LVESV by >0<15%), Gr.2 (n=38): responders (decrease in LVESV by >15<30%). At baseline, in the "best" timing and in the "end" timing (November 2020), parameters of echocardiography, NT-proBNP, epinephrine, norepinephrine (NAdr), IL 1β, 6, TNF-α, C-reactive protein, matrix metalloproteinase 9, tissue inhibitor of matrix metalloproteinases 1 in plasma were studied. Survival was estimated by Kaplan-Meier method. Logistic regression was used to assess relationship of studied factors with CRT efficacy, and Cox regression with survival.

Results. In Gr.1, greater heart failure functional class was revealed (p=0.042). In Gr.1, there was less reverse cardiac remodeling in the "best" timing and greater pulmonary artery systolic pressure (p=0.029), NT-proBNP (p=0.020) in the "end" timing. Immune activation and imbalance of fibrogenesis were found across all time points of the study. In Gr.1, increase in NAdr level was revealed only in the "end" timing (p=0.017), but in Gr.2 it already was in the "best" timing (p=0.003). Correlations of NAdr "best" with ΔLVESV (r=-0.245; p=0.038), Δ left ventricle end-diastolic volume (LVEDV) (r=-0.293; p=0.013) in general group; and with IL-1β "best" (r=0.363; p=0.032) , TNF-α "best" (r=0.360; p=0.034) in responders group were registered. Responder's survival was the best only at 2 and 3 years after CRT implantation, with comparable survival between groups in subsequent years. In Gr.1, significant factors associated with 2-3-year survival were LVEDV "best" (RR 0.831 (0.713-0.967), p=0.017), LVESV "best" (RR 1.245 (1.040-1.492), p=0.017); in Gr.2, NT-proBNP "end" (RR 1.001 (1.000-1.001), p=0.024) related to 10-year survival in the absence of significant factors.

Conclusion. Comparable 10-year survival rate of non-progressors and responders is probably due to immune, sympathetic-adrenal activation, fibrogenesis imbalance. In non-progressors group CRT response can be assessed as positive due to significant reverse cardiac remodeling and survival comparable to responders and associated with NT-proBNP level.

Key words: cardiac resynchronization therapy; nonprogressors; survival; immune inflammation; fibrogenesis; neurohumoral; sympathetic-adrenal activation

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Cardiac resynchronisation therapy (CRT) is a modern and effective treatment for patients with chronic heart failure (CHF) with a dilated QRS complex against the background of optimal drug therapy [1]. Despite ever-changing guidelines on the selection of patients for implantation of CRT devices, about 30% of patients do not respond favourably to cardiac resynchronisation [2]. It is possible that the high percentage of 'non-responders' is overestimated and is due to the early fixed timing and the different criteria used to assess the effectiveness of CRT, among which are clinical parameters, exercise tolerance, left ventricular ejection fraction (LVEF), and left ventricular end-systolic volume (LVESV). A multimarker approach with integrated assessment of echocardiographic (Echo) and laboratory parameters is possible [3]. A more frequent criterion for the effectiveness of CRT is a reduction in LVESV of more than 15% of baseline. The scientific literature discusses 5 types of response to CRT: reverse responders, non-responders, non-progressors, responders, and super-responders, based on reverse cardiac remodelling over time [4], although there is no absolute relationship between reverse cardiac remodelling on CRT and survival [5-7]. Comparable 5-year survival rates between 'non-progressors' and 'responders' have previously been shown [8], but the bio-

chemical aspect of the suboptimal response to CRT and its association with long-term survival remain unexplored, making our study relevant.

The aim of the study was to evaluate the 10-year survival, clinical and biochemical status of CRT responders and non-responders using biomarkers of fibrosis, neurohumoral, immunological and sympatho-adrenal activation.

METHODS

Eighty consecutive patients with implanted CRT devices from the "Register of Cardiac Resynchronization Therapy Operations Performed" (Database Registration Certificate No. 2010620077 dated February 1, 2010) were included in the study from 2004 to 2019. The mean age of the patients was 58.9±10.1 years, of whom 72 (90%) were men, and 58 (72.5%) had cardiomyopathy of ischemic genesis. CRT devices with cardioverter-defibrillator function were implanted in 57 (71.3%) patients, only in 1 patient a quadripolar electrode was implanted. The diagnosis of CHF was made based on clinical guidelines for the diagnosis and treatment of CHF [9]. The St Mary's Hospital (London) protocol was used to refer patients for implantation of CRT, highlighting basic and additional criteria. The main criteria included: CHF class II/IV (NYHA), optimal drug therapy, LVEF <35% (measured by Simpson), exclusion of reversible causes of systolic heart failure, optimal revascularization. The additional criteria are divided into major and minor. Major additional criteria include signs of intraventricular dyssynchrony determined by tissue spectral Doppler: increased intraventricular mechanical contraction variance >55 ms; signs of combined intra- and interventricular dyssynchrony: sum of intra- and interventricular variance >100 ms (with variance defined as the time difference between earliest and latest segment contraction). Minor additional criteria include evidence of intraventricular dyssynchrony - intraventricular variance >40 ms; evidence of interventricular dyssynchrony - interventricular variance >40 ms; decreased left ventricular filling time <40% of mean cycle (transmitral blood flow Doppler); aortic pre-ejection period >140 ms (aortic blood flow Doppler); interventricular mechanical delay >40 ms (aortic and pulmonary blood flow Doppler); QRS>130 ms. For implantation of CRT devices, all basic criteria and some additional criteria must be met: 2 major or 1 major + 3 minor or 4 minor [10]. The use of the St. Mary's Hospital protocol did not contravene current guidelines for selecting patients for implantation of CRT devices.

The patients during Registry underwent control examinations at baseline, after 1, 3, 6, and then every 6 months thereafter. If necessary, the parameters of the CRT devices were optimized during the visits. The presented analysis retrospectively included baseline data, the visit with the best response to CRT, verified by the maximum reduction of LVESV against CRT, as well as at the study endpoint - a cutoff in November 2020 was made. If the patient died before November 2020,

Table 1.

Clinical characteristics of patients

Indicator	Group I non-progressors (n=42)	Group II respondents (n=38)	p
MFP, months	44.9±36.7	63.9±47.5	0.051
MBRT on CRT, months	19.3±23.4	27.1±28.4	0.107
Average age, years	56.8±10.7	61.1±9.0	0.057
Men, n (%)	38 (90.5)	34 (89.5)	0,881
CAD, n (%)	30 (71.4)	28 (73.7)	0.821
PICS, n (%)	22 (52.4)	18 (47.4)	0.654
CABG, n (%)	5 (11.9)	3 (7.9)	0.550
PCI, n (%)	17 (40.5)	15 (39.5)	0.927
II FC HF (NYHA), n (%)	19 (45.2)	22 (57.9)	0.042
III FC HF (NYHA), n (%)	15 (35.7)	16 (42.1)	
IV FC HF (NYHA), n (%)	8 (19.1)	0 (0)	
AH, n (%)	32 (76.2)	27 (71.1)	0.602
AF, n (%)	25 (59.5)	23 (60.5)	0.916
RFA AV, n (%)	11 (26.2)	12 (31.6)	0.595
DM, n (%)	8 (19.0)	10 (26.3)	0.437
Obesity, n (%)	24 (57.1)	19 (50.0)	0.552
BMI, kg/m^2	30.9±6.9	30.9±5.5	0.991
QRS duration, ms	152.1±34.5	141.1±43.5	0.223
CLBBB, n (%)	24 (57.1)	18 (47.4)	0.382
AAD*, n (%)	20 (47.6)	16 (42.1)	0.554
MRA, n (%)	37 (88.1)	33 (86.4)	0.578
Diuretics, n (%)	29 (74.4)	21 (58.3)	0.141
Ca-channel blockers$^@$, n (%)	6 (15.4)	6 (16.7)	0.880
BAB, n (%)	35 (83.3)	33 (86.8)	0.775
Digoxin, n (%)	9 (21.4)	8 (21.1)	0.930
Anticoagulants, n (%)	19 (48.7)	21(58.3)	0.404
Antiplatelets, n (%)	16 (38.1)	16 (42.1)	0.765
ACEI or ARB, n (%)	38 (90.5)	33 (86.8)	0.434
Statins, n (%)	15 (38.5)	14 (38.9)	0.970

Note: MFP - mean follow-up period; MBRT - mean best response time; CAD - coronary artery disease; PICS - postinfarction cardiosclerosis; CABG - coronary artery bypass grafting; PCI - percutaneous coronary intervention; FC HF (NYHA) - New York classification class of heart failure; AH - arterial hypertension; AF - atrial fibrillation; RFA-AV - radiofrequency ablation of the atrio-ventricular junction; DM - diabetes mellitus; BMI - body mass index; CLBBB - complete left bundle branch block; MRA - mineralocorticoid receptor antagonists; AADs-antiarrhythmic drugs; BAB - β-adrenoblockers; ACEI - angiotensin-converting enzyme inhibitors; ARB - angiotensin receptor blockers. *-amiodarone, sotalol; $^@$-amlodipine, felodipine.

Table 2.

Dynamics of 6-minute walking test and echocardiographic indices

Indicator		Group I non-progressors (n=42)	Group II respondents (n=38)	P
6MWT, m	initially	291.0±120.2	328.9±78.1	0.144
	best	349.6±97.5	366.5±83.3	0.441
	end	308.7±140.7	327.1±101.3	0.548
Pin/best; Pin/end; Pbest/end		0.003; 0.518; 0.015	0.015; 0.461; 0.014	
LA, mm	initially	50.4±6.2	52.8±6.9	0.114
	best	49.5±7.3	49.8±6.9	0.858
	end	51.1±8.2	51.2±8.4	0.963
Pin/best; Pin/end; Pbest/end		0.251; 0.500; 0.049	<0.001; 0.064; 0.038	
PP, ml	initially	90.4±47.3	90.7±37.2	0.976
	best	89.0±40.9	81.6±32.3	0.410
	end	98.8±47.6	82.5±35.1	0.097
Pin/best; Pin/end; Pbest/end		0.055; 0.199; 0.039	0.001; 0.090; 0.101	
RV, mm	initially	31.6±5.3	30.8±4.7	0.445
	best	30.7±4.7	29.5±4.0	0.213
	end	32.8±6.1	30.6±4.2	0.064
Pin/best; Pin/end; Pbest/end		0.032; 0.189; 0.004	0.003; 0.738; 0.006	
LV ESD, mm	initially	58.5±9.3	54.7±8.8	0.159
	best	56.0±7.8	51.3±7.2	0.046
	end	57.6±9.6	52.7±9.1	0.067
Pin/best; Pin/end; Pbest/end		0.001; 0.451; 0.214	0.001; 0.352; 0.113	
LV EF, mm	initially	67.7±7.8	66.5±6.8	0.468
	best	66.8±7.8	62.8±6.7	0.014
	end	68.2±8.4	65.8±7.7	0.184
Pin/best; Pin/end; Pbest/end		0.007; 0.183; 0.004	<0.001; 0.215; <0.001	
LV ESV, ml	initially	165.3±54.0	158.4±46.6	0.540
	best	151.3±49.9	124.6±38.2	0.009
	end	162.0±55.4	145.3±54.1	0.181
Pin/best; Pin/end; Pbest/end		<0.001; 0.615; 0.013	<0.001; 0.003; <0.001	
LV EDV, ml	initially	238.9±61.4	229.8±54.0	0.485
	best	230.2±60.6	199.7±48.5	0.009
	end	243.7±68.1	225.1±60.9	0.204
Pin/best; Pin/end; Pbest/end		0.001; 0.238; 0.005	<0.001; 0.287; <0.001	
LV EF, %	initially	32.1±8.1	32.0±7.4	0.946
	best	35.4±8.8	38.7±6.6	0.063
	end	34.2±9.2	37.0±8.9	0.184
Pin/best; Pin/end; Pbest/end		<0.001; 0.003; 0.027	<0.001; <0.001; 0.057	
SPPA, mmHg	initially	47.5±12.7	46.4±14.9	0.760
	best	42.0±13.2	39.4±10.8	0.419
	end	45.9±13.6	39.3±9.4	0.029
Pin/best; Pin/end; Pbest/end		0.005; 0.231; 0.014	0.005; 0.021; 0.318	

Hereinafter: best - term of best response on cardiac resynchronisation therapy, end - study endpoint, 6MWT - 6-minute walk test; LA - left atrium; RA - right atrium; RV - right ventricle; ESD - end-systolic dimension; LV - left ventricle; EDD - end-diastolic dimension, ESV - end-systolic volume, EDV - end-diastolic volume, EF - ejection fraction; SPPA - systolic pressure in pulmonary artery

data from the visit preceding the death were included in the study. The absence of a fixed term made it possible to maximally assess the best result of CRT, verified by the greatest reduction of LVESV, considering individual adaptive capabilities of patients. The November 2020 cutoff allowed us to assess the dynamics of the studied factors as far removed as possible from the baseline to evaluate their relationship with survival.

Functional class (FC) was determined considering the 6-minute walk test and clinical criteria of NYHA classification (NYHA FC). EchoCG was performed on Philips IE-33 (USA) with assessment of parameters according to standard criteria: left atrial size and right atrial volume, left ventricular (LV) end-systolic (ESD) and end-diastolic dimensions (EDD), LV ESV and LV end-diastolic volumes (EDV), LVEF, systolic pressure in pulmonary artery (SPPA). Plasma levels of adrenaline (Adr), noradrenaline (NAdr), N-terminal fragment of natriuretic peptide (NT-proBNP), interleukins (IL)-1β, 6, tumor necrosis factor α (TNF-α), matrix metalloproteinase 9 (MMP-9) and tissue inhibitor of matrix metalloproteinases (TIMP-1) were tested by solid-phase chemiluminescence immunoassay (sandwich method) on an IMMULITE 1000 analyzer (SiemensDiagnostics, USA). The determination of the highly sensitive C-reactive protein fraction (CRP) in serum was performed by immuno-turbidimetric method using C-REACTIVE PROTEIN hs assay kits (BioSystems, Spain) on a Clima MC-15 analyser (Spain). Patients signed an informed consent to participate in the study that was approved by the ethics committee.

Statistical analysis was performed using the SPSS 21 software package (SPSS Inc., Chicago, IL, USA). Normality of the distribution was assessed using the Kolmogorov-Smirnov

method. With a normal distribution, results are presented as M±sd, where M is the mean, sd is the standard deviation, with a distribution other than normal, the median and interquartile range (Me [25;75]). Pearson Chi-square test was used to analyze qualitative data in unrelated groups. For quantitative comparisons of the unrelated groups, Student's t-test was used for normal distribution, Mann-Whitney for non-normal distribution, and paired Student's t-test or Wilcoxon's t-test for related groups. Differences were considered significant at $p<0.05$. Bonferroni correction was used for multiple comparisons; the significant level of difference was $p<0.017$. Survival was assessed by the Kaplan-Meier method. Logistic regression was used to evaluate the relationship between the factors under study and the efficacy of CRT, and Cox regression was applied to the survival rate. The relationships between the factors under study were assessed using Spearman correlation analysis.

RESULTS

Two groups were distinguished in the term of best response: Group 1 (n=42) were non-progressors (with a decrease in LVESV > 0% but < 15%), and Group 2 (n=38) were responders (with a decrease in LVESV >15% but < 30%). Comparison of clinical characteristics revealed trends toward older age (p=0.057) and longer mean follow-up period (p=0.051) of group 2 patients. Group 1 patients had significantly higher FC of heart failure. Clinical characteristics of the study groups are presented in Table 1. According to the 6-minute walk test, the distance walked increased significantly at the time of best response and decreased at the study endpoint in both groups. The results of the 6-minute walk test did not differ significantly between the studied groups at all points of the study.

Baseline Echo parameters did not differ in the studied groups. At the time of best response in both groups their significant positive dynamics was observed, but less pronounced in Group 1: there was no dynamics of left and right atrial parameters, there were big LVESD, LVEDD, LVESV, LVEDV. The degree of change in Echo parameters was more pronounced in the responders' group. At the study endpoint, both groups showed an increase in the investigated Echo parameters with no differences between the groups, except for SPPA, which was significantly higher in Group 1. A significant increase in the right atrium and SPPA compared with the best response time was detected only in Group 1. The dynamics of Echo parameters are presented in Table 2.

At all study points, catecholamine levels in the groups were within the reference values. There were no group dynamics and no differences between groups in Adr concentrations. Although there were no significant differences in basal NAdr levels between the groups, at the time of best response only Group 2 showed a highly significant threefold increase in Nadr concentration, which was almost twofold higher than in Group 1. At the study endpoint, while there was a significant increase in NAdr levels in Group 1, there was no significant difference between the groups. In general, we can note an earlier increase in NAdr level in Group 2, already at the time of the best response, while in Group 1 the increase in NAdr level was noted only at the end of the study. The Spearman correlation analysis method in the overall group revealed an association of NAdr level with ΔLVESV (r=-0.245; p=0.038), ΔLVEDV (r=-0.293; p=0.013), and in the responders group with IL-1β (r=0.363; p=0.032), TNF-α (r=0.360; p=0.034) at the time of best response (Figure 1).

At all study points, NT-proBNP levels were significantly higher than the reference values. Despite reverse cardiac remodeling, there was no significant change in NT-proBNP level in either group; however, at the end of the study, its concentration was significantly higher in Group 1.

TNF-α concentrations at baseline and endpoint were higher than the reference values in both groups. At the end of the study, its levels were significantly higher in Group 1 compared to the term of the best response. At all study points, TNF-α levels were comparable between the groups.

The levels of IL-1β were within the reference values. In Group 1, its concentration significantly decreased at the

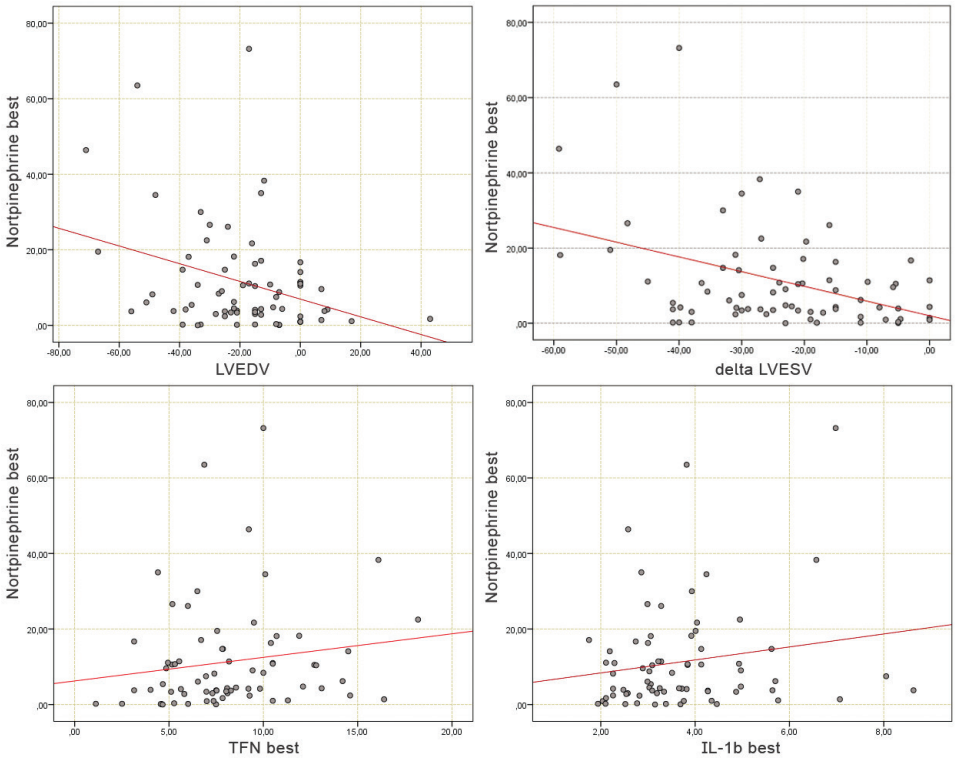

Fig. 1. Correlations of noradrenaline with EchoCG parameters and biomarkers of immune inflammation in the total group.

time of the best response and increased at the endpoint. In Group 2, there was a significant increase in its concentration at the end of the study. There were no differences in IL-1β concentrations between the groups at all study points. IL-6 concentrations were also within the reference values at all study points. Basal concentrations of IL-6 were significantly higher in Group 2. While there were no changes in IL-6 levels in Group 1, Group 2 showed a decrease in its concentration at the time of the best response and at the end of the study.

Only the baseline CRP level in Group 2 was within the reference values and significantly lower compared to

Table 3.

Dynamics of biomarkers in the study groups.

Indicator		Reference values	Group I non-progressors (n=42)	Group II respondents (n=38)	P
Adr, ng/ml	initially	0.018-6.667	0.9[0.1;2.3]	0.9[0.2;3.2]	0.741
	best		1.3[0.3;2.2]	1.2[0.6;2.7]	0.573
	end		1.4[0.5;3.0]	1.2[0.6;2.7]	0.712
Pin/best; Pin/end; Pbest/end			0.465; 0.629; 0.168	0.492; 0.209; 877	
NAdr, ng/ml	initially	0.093-33.333	2.9[0.1;11.6]	3.0[0.6;11.4]	0.582
	best		4.2[1.3;10.7]	9.1[3.7;22.5]	0.003
	end		10.3[3.6;16.4]	12.8[6.6;24.3]	0.264
Pin/best; Pin/end; Pbest/end			0.503; 0.184; 0.017	0.003; 0.136; 0.807	
NT-proBNP, pg/ml	initially	Up to 125	2752.0[977.0;5789.0]	2236.0[1429.0;3986.0]	0.643
	best		1784.0[723.3;4301.5]	1220.0[542.5;3208.0]	0.229
	end		2118.0[700.5;5286.5]	1051.0[555.0;2983.5]	0.020
Pin/best; Pin/end; Pbest/end			0.108; 0.251; 0.264	0.605; 0.938; 0.888	
IL-1β, pg/ml	initially	0-5	3.8[2.8;4.3]	3.4[2.4;4.7]	0.897
	best		3.7[2.9;4.6]	3.1[2.7;4.2]	0.888
	end		4.4[3.9;4.9]	4.4[3.7;5.0]	0.647
Pin/best; Pin/end; Pbest/end			0.210; 0.001; 0.009	0.109; 0.091; <0.001	
IL-6, pg/ml	initially	0-9.7	3.0[2.1;4.2]	4.3[3.4;7.8]	0.016
	best		3.3[2.4;4.0]	3.3[2.3;4.6]	0.654
	end		3.2[2.2;3.9]	2.6[2.0;3.7]	0.329
Pin/best; Pin/end; Pbest/end			0.092; 0.702; 0.092	0.108; 0.009; 0.007	
TNF-α, pg/ml	initially	<8.11	8.6[5.8;11.2]	8.7[4.1;10.6]	0.491
	best		7.8[5.5;10.5]	7.6[5.7;10.0]	0.960
	end		9.5[7.0;11.4]	8.2[6.5;9.9]	0.109
Pin/best; Pin/end; Pbest/end			0.945; 0.272; 0.037	0.945; 0.891; 0.628	
CRP, mg/ml	initially	<3.0	5.2[3.4;9.3]	2.5[1.2;7.0]	0.033
	best		4.1[2.4;8.4]	4.3[2.5;6.2]	0.704
	end		4.8[2.7;9.7]	6.1[2.7;11.9]	0.360
Pin/best; Pin/end; Pbest/end			0.520; 0.826; 0.670	0.580; 0.019; 0.034	
MMP-9, ng/ml	initially	2.0-139.4	148.9 [121.3;212.6]	157.9[134.4;189.0]	0.774
	best		148.9[114.9;188.9]	157.4[123.4;226.1]	0.280
	end		190.2[147.1;252.0]	182.9[140.6;257.7]	0.914
Pin/best; Pin/end; Pbest/end			0.314; 0.277; 0.012	0.789; 0.107; 0.058	
TIMP-1, ng/ml	initially	92-116	305.7[207.1;465.3]	226.3[160.8;363,.]	0.317
	best		225.1[168.8;339.9]	213.6[152.8;253.7]	0.313
	end		146.2[114.3;204.1]	153.6[121.3;202.6]	0.995
Pin/best; Pin/end; Pbest/end			0.113; <0.001; <0.001	0.834; 0.005; 0.001	

Note: Adr - adrenaline; NAdr - noradrenaline; IL - interleukin; TNF-α - tumor necrosis factor α; CRP - C-reactive protein; NT-proBNP - N-terminal fragment of natriuretic peptide; MMP-9 - matrix metalloproteinase 9; TIMP-1 - tissue inhibitor of matrix metalloproteinase 1.

Group 1. In the remaining study points, CRP concentrations were higher than the reference values and did not differ between the groups. There were no changes in CRP in Group 1, while in Group 2 there was a significant increase in its concentration at the time of the best response and at the endpoint.

The concentrations of MMP-9 and TIMP-1 in the groups were higher than the reference values. There were no differences in fibrosis biomarkers between the groups. At the endpoint, the levels of MMP-9 significantly increased in Group 1, in Group 2 there was a tendency for its concentration to increase, indicating an increase in the activity of collagenolytic processes in the groups. TIMP-1 levels significantly decreased in the dynamics in the studied points in both groups, indicating a decrease in the activity of collagen-forming processes. The dynamics of the studied biomarkers are presented in Table 3.

Logistic regression was applied to identify factors associated with the effectiveness of the CRT. According to the results of multivariate analysis, which included indices that differed significantly between the groups: in the timing of the best response of LVEDD, LVESD, LVEDV, LVESV, NAdr, by direct stepwise selection none of the factors was associated with efficacy with CRT.

The Kaplan-Meier method was used to estimate survival in the groups for 10 years after implantation of resynchronizing devices. There was a better survival in the responders' group at the 2nd (69.8% vs 89.2%; Log Rank test=0.043) and 3rd year (61.8% vs 83.1%; Log Rank test=0.040) after implantation with comparable survival to Group 1 in the other years. The 10-year group survival rate was 32.3% in Group 1 versus 44.6% in Group 2 (Log Rank test=0.188) (Figure 2).

Cox regression was performed to identify factors associated with survival. In Group 1, the significant factors associated with 2 to 3-year survival were the timing of the best response LVEDV (OR 0.831 (0.713-0.967), p=0.017), LVESV (OR 1.245 (1.040-1.492), p=0.017). The univariate analysis in Group 1 identified factors associated with mortality over 10 years: term of best response, endpoint values of LVESD, LVEF, SPPA, and NT-proBNP. Subsequently, these factors were included in a multivariate analysis, according to which only NT-proBNP level at the end of the study had a significant association with 10-year survival. In Group 2, the single-factor analysis added IL-6 level in addition to the factors of best response time, endpoint LVESD, LVEF, SPPA, and NT-proBNP. However, in the multivariate analysis, none of the factors was associated with 10-year survival (Table 4).

DISCUSSION

In scientific studies, a group of patients with a LVESV decrease of less than 15% on the background of CRT is classified as non-responders, which does not correspond to reality, in our opinion, and overestimates the percentage of non-responders in the assessment of CRT efficacy. Both groups we studied demonstrated a significant reduction of heart chambers, improvement of its contractility in dynamics, and an increase of exercise tolerance. Even a suboptimal response to CRT, no clinical deterioration and no further decline in LV systolic function indicate stabilization. This type of response to CRT is not negative. Non-progressors are also a favorable response to CRT, which must be considered when evaluating its effectiveness.

Today, there is no consensus on the time frame for evaluating the effectiveness of CRT. As a rule, the evaluation of the effectiveness of CRT is carried out at fixed times - after 6 months, 24 months, 3 years, which underestimates the true percentage of respondents. As studies have shown, rapid improvement in clinical and functional parameters is not a marker of successful CRT, and a lack of significant improvement in Echo during the first year of CRT is not a criterion for poor response. The response to CRT is very individual and depends largely on the preservation of the patient's adaptive capabilities. The average terms of the best response to CRT in our study groups are the 2nd and 3rd year of cardiac resynchronization. The approach of personalized of the efficacy of CRT we use, considering the best term verified by the maximum reduction in LVESV, allows us to maximize the evaluation of a favourable response to CRT without underestimating the number of responders. The REVERSE (REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction study) showed maximum improvement by 2 years of CRT [11]. Our results coincide with those of the REVERSE study.

The mechanisms of the effects of CRT on the physiological processes in the body of a CHF patient are not fully understood. Given the complex pathophysiological continuum of CHF, to investigate possible mechanisms of suboptimal response to CRT, we examined biomarkers of key links in the pathogenesis of CHF: immune inflammation (IL-1β, 6, TNF-α, CRP), neurohumoral (NT-proBNP) and sympatho-adrenal (catecholamines) activation, fibroin formation (MMP-9, TIMP-1).

The better effect of CRT in both groups may have been compromised by the high degree of immune activation characteristic of CHF [12], which correlates with disease severity and poor prognosis [13]. Hyperexpression of the proinflammatory cytokines IL-1β, 6 and TNF-α, regardless of the etiology of CHF, is accompanied by mitochondrial dysfunction, negative inotropic effects, left ventricular remodelling [14] and progressive fibrosis [15]. The high activity of immune inflammation in the groups

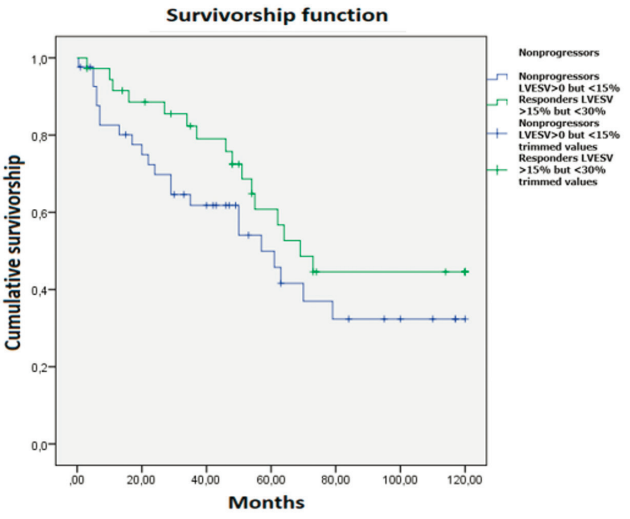

Fig. 2. 10-year survival of non-progressors and responders (Log Rank test=0.188).

we analyzed was evidenced by TNF-α and CRP levels exceeding the reference values. The role of CRP and its level reduction [16, 17], as well as other cytokines in achieving a favorable response to CRT is actively discussed in the literature [18]. In our univariate logistic regression analysis, IL-6 levels were among the factors associated with CRT efficacy. We should note the comparable dynamics of proinflammatory cytokine levels against the background of CRT in the groups under study.

The association of proinflammatory cytokines with the concentration of natriuretic peptides (NPs) has been established [19, 20], the prognostic value of which is emphasized by meta-analyses [21]. The results of our Cox regression in the non-progressors group confirm the prognostic significance of NT-poBNP level at the endpoint associated with 10-year survival. Earlier multicenter studies have established an association between response to CRT and levels of NPs [22-24]. In our work, high NT-proBNP levels at all study points are indicative of the severity of the patients analyzed. The absence of NT-proBNP dynamics in the groups may be due to a wide range of its values, a consequence of a compensatory response to sympatho-adrenal activation. Less reverse cardiac remodeling in Group 1 patients was associated with higher NT-proBNP concentrations.

It is known that cytokines through the activation of cell signaling pathways TGF-β/Smad and Notch [25, 26] promote cardiomyocyte apoptosis, increase MMPs synthesis, which leads to collagen degradation, reconstruction of extracellular cardiac matrix, dilatation of heart cavities, CHF progression. The activity of MMPs is counteracted by TIMPs, which enhance collagen formation. High concentrations of MMP-9 [27, 28] and TIMP-1 [29] have been associated with the severity of CHF; however, the available information concerning their prognostic value is controversial [30]. High levels of MMP-9 and TIMP-1 in the groups we analyzed at all study points confirm the severity of the patients included in the study. The increase of MMP-9 levels and decrease of TIMP-1 level in dynamics may indicate imbalance of fibrosis and intensification of collagenolytic processes in myocardium. In general, one can note comparable activity of extracellular cardiac matrix reconstruction processes in the studied groups.

One of the key links in the pathogenesis of CHF, regardless of its etiology, is sympathetic hyperactivation, which in the first stages of CHF is compensatory in nature and is aimed at maintaining the pump function of the heart. The main mediator of sympathetic activation is NAdr, the predictive significance of which in CHF was first shown by J.N.Cohn et al. (1984) [31], and then by Val-HeFt [32], ADMIRE-HF [33]. The complex process of dysfunction and then depletion of sympathetic structures in the myocardium in CHF is accompanied by an increase in adrenal catecholamine synthesis entering the bloodstream and replacing missing sympathetic influences. The transition of heart rhythm regulation from sympathetic to adreno-humoral level takes place. The significant, almost threefold, increase in NAdr levels at the time of best response in the respondent group is probably compensatory and may contribute in the early stages to better cardiac remodelling. This can be evidenced by the correlations of the NAdr level with the degree of change in LVESV and LVEDV revealed at the time of the best response. It was the LVESV and LVEDV in the best response time according to Cox regression data that were associated in Group 1 with a 2-3-year survival rate. However, with prolonged exposure, the metabolic effects of elevated NAdr levels can reduce the efficacy of CRT by increasing myocardial dysfunction. It has been shown in experimental studies that infusion of NAdr is accompanied by the expression of the main regulator of cellular aging, p53 protein, which contributes to cardiac dysfunction by regulating the cell cycle or apoptosis [34]. Through p53 signalling, NAdr induces endothelial inflammation of the heart by activation of intercellular adhesion molecule-1 (ICAM1) and expression of integrin in endothelial cells, macrophages, leading to tissue damage, proliferation of fibroblasts, transforming into myofibroblasts and causing myocardial fibrosis. Sympatho-adrenal activation by expression of β2-adrenoreceptors is accompanied by increased production of reactive oxygen species [35], synthesis and secretion of growth factors and cytokines in cardiomyocytes, activating cardiac fibroblasts and increasing collagen synthesis [36]. Cytokines and other inflammatory mediators are known to enhance sympathetic activation through various cellular mechanisms [37]. The correlations of NAdr with IL-1β and TNF-α we found at the

Table 4.

Relationship of investigated factors to 10-year survival according to Cox regression results in patient groups.

	Univariate analysis		Multivariate analysis	
Factors	HR (95% CI)	Log-rank P value	HR (95% CI)	Log-rank P value
Group I non-progressors (n=42)				
Term best	0.970 (0.947-0.993)	0.012	0.991 (0.922-1.066)	0.814
CSWLend	1.062 (1.000-1.127)	0.049	1.040 (0.902-1.199)	0.588
LVEFend	0.939 (0.889-0.993)	0.026	0.917 (0.802-1.049)	0.207
SPPAend	1.055 (1.017-1.095)	0.004	0.915 (0.817-1.024)	0.122
NT-proBNPend	1.000 (1.000-1.000)	0.001	1.001 (1.000-1.001)	0.024
Group II respondents (n=38)				
Term best	0.949 (0.918-0.982)	0.002	0.907 (0.801-1.027)	0.125
CSWLend	1.077 (0.994-1.164)	0.070	0.897 (0.769-1.045)	0.162
LVEFend	0.939 (0.881-1.001)	0.054	1.030 (0.875-1.213)	0.722
SPPAend	1.055 (0.994-1.119)	0.079	1.068 (0.833-0.370)	0.602
NT-proBNPend	1.001 (1.000-1.001)	<0.001	1.001 (1.000-1.002)	0.161
IL-6end	1.582 (1.059-2.363)	0.025	0.304 (0.054-1.728)	0.179

time of best response in the respondent group confirm the relationship between immune and sympathetic activation.

Thus, the observed comparable 10-year survival of non-progressors and responders is probably due to immune, sympatho-adrenal activation, and fibrosis imbalance. The response to CRT in non-progressors can be assessed as positive due to significant reversal of cardiac remodeling, comparable to responders' survival associated with NT-proBNP levels.

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