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RELATIONSHIP BETWEEN LEFT VENTRICULAR MECHANICAL DYSSYNCHRONY WITH CARDIAC RESYNCHRONIZATION THERAPY RESPONSE IN CHRONIC HEART FAILURE PATIENTS WITH LEFT BUNDLE BRANCH BLOCK

S.V.Agafonkin, T.A.Atabekov, A.I.Mishkina, S.N.Krivolapov, S.I.Sazonova, M.S.Khlynin, K.V.Zavadovskiy, R.E.Batalov, S.V.Popov

Cardiology Research Institute, branch of the Federal State Budgetary Scientific Institution "Tomsk National Research Medical Center of the Russian Academy of Sciences", Russia, Tomsk, 111A Kievskaya str.

Aim. To investigate the relationship between left ventricular (LV) mechanical dyssynchrony with cardiac resynchronization therapy (CRT) response in chronic heart failure (CHF) pts with left bundle branch block.

Methods. Forty-nine pts (male - 34 [69.4%], average age 58.3±11.4 years) with sinus rhythm, permanent left bundle branch block with QRS duration ≥150 ms and New York Heart Association (NYHA) II-III functional class of CHF were included in the study. In addition to full examination, myocardial perfusion scintigraphy (MPS) and gated blood pool single-photon emission computed tomography (gBPS) were performed before and 6 months after CRT devices with cardioverter-defibrillator function implantation. Pts were considered as responders to CRT if they fulfilled after 6-month follow-up the following combined criteria: NYHA FC improvement ≥1 class + LV end systolic volume decrease >15% or NYHA FC improvement ≥1 class + LV ejection fraction improvement >5%.

Results. The 1st and 2nd groups included 35 (71.4%) and 14 (28.6%) pts with and without response to CRT respectively. Groups were comparable in terms of pre-CRT implantation clinical and instrumental parameters, except for MPS and gBPS parameters. The multivariate logistic regression had shown that only Δinterventricular dyssynchrony (adjusted odds ratio [OR] 1,0349; 95% confidence interval [CI] 1.0075-1,0631; p=0.01) and phase standard deviation of the anterior LV wall (OR 1.0669; 95% CI 1.0118-1.1251; p=0.01) were independently related with CRT response. An increase in the prognostic coefficient, calculated using the Δinterventricular dyssynchrony and phase standard deviation of the anterior LV wall, more than 0.67 was a predictor of CRT response (area under the curve 0.918; sensitivity 85.71; specificity 85.71; p <0.001).

Conclusion. The mechanical dyssynchrony assessed by MPS and gBPS is associated with CRT response. According to our predictive model, an increase in prognostic coefficient more than 0.67 is a predictor of CRT response.

Key words: left bundle branch block; chronic heart failure; cardiac resynchronization therapy; mechanical dyssynchrony of the left ventricle

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Corresponding author: Sergey Agafonkin, E-mail: asv@cardio-tomsk.ru

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S.V.Agafonkin - ORCID ID 0000-0002-7358-6386, T.A.Atabekov - ORCID ID 0000-0003-2645-4142, A.I.Mishkina - ORCID ID 0000-0001-9453-1635, S.N.Krivolapov - ORCID ID 0000-0001-8121-8287, S.I.Sazonova - ORCID ID 0000-0003-2799-3260, M.S.Khlynin - ORCID ID 0000-0002-9885-5204, K.V. Zavadovskiy - ORCID ID 0000-0002-1513-8614, R.E.Batalov - ORCID ID 0000-0003-1415-3932, S.V.Popov - ORCID ID 0000-0002-9050-4493

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Nowadays heart failure (HF) is a serious public health problem due to the high risk of mortality and morbidity and the poor quality of life of patients [1]. Cardiac resynchronization therapy (CRT) is a recognized treatment option for patients with chronic HF, especially in patients with reduced left ventricular ejection fraction (LVEF) and left bundle branch block [2]. According to the recommendations on pacing and CRT, the main selection criteria for cardiac resynchronization therapy in symptomatic patients with HF are low LVEF and complete left bundle branch blockade (LBBB) with QRS complex duration more than 130 ms despite optimal drug therapy [3]. QRS prolongation (120 ms or more) is found in 14.0-47.0% of patients with CHF, and ventricular conduction disturbance, most commonly LBBB, is present in about one-third of patients with HF, leading to ventricular mechanical dyssynchrony

(MD) [4, 5]. In most patients, CRT restores impaired left ventricular (LV) contractile function. These patients are categorized as CRT responders. Nowadays the main predictors of a positive response to CRT are: nonischemic HF, female gender, QRS complex dilation ≥150 ms with LBBB morphology. Nevertheless, no improvement in cardiac contractile function and clinical status is observed in 30% of patients [6].

Several studies have shown that a method of assessing cardiac contractile function using transthoracic echocardiography, magnetic resonance, computed tomography, and single-photon emission computed tomography can play a key role in predicting response to CRT [7-10]. However, according to the multicenter PROSPECT study, the use of standard echocardiographic parameters of dyssynchrony was not a reliable predictor of response to CRT [11]. The use of magnetic resonance imaging, although highly accurate and informative, is limited by high cost, complexity of cardiac protocols, and the presence of operator-dependent techniques [12]. At the same time, myocardial perfusion scintigraphy (MPS) and radionuclide tomoventriculography (RTVG) are simple techniques that have higher reproducibility and can detect cardiac ventricular MD, blood flow abnormalities and myocardial scarring [13]. The prognostic value of MD assessed by MPS remains controversial. In several studies, MD correlates with a positive response to CRT in patients with CHF of ischemic and non-ischemic etiology [14, 15]. However, another work showed the lack of prognostic significance of MD in patients with ischemic cardiomyopathy [16, 17]. But there are few papers on the combined assessment of reverse remodeling-related factors that can be used to improve patient selection for CRT [18].

Therefore, the aim of our study was to identify the relationship between MD LV and response to CRT in patients with LBBB and CHF.

METHODS

Patient population and study design

This clinical, non-randomized, open-label, prospective study enrolled patients with indications for CRT according to ESC guidelines [3]. Inclusion and exclusion criteria were defined according to the research project «Single-photon Emission Computed Tomography for Prediction and Evaluation of Cardiac Resynchronization Therapy Efficacy in Chronic Heart Failure Patients,» ClinicalTrials.gov, NCT03667989). Patients included in the study met the following criteria: presence of HF (ischemic or nonischemic etiology), sinus rhythm, persistent LBBB with QRS complex duration ≥150 ms, New York Heart Association (NYHA) functional class (FC) of HF II-III, LVEF ≤35%, and optimal drug therapy for at least 3 months. Patients with NYHA HF I, IV FC, decompensated HF, recent myocardial infarction (less than 3 months), right bundle branch block, previously implanted pacemaker or cardioverter-defibrillator, severe comorbidities, cognitive impairment, indications for revascularization and heart transplantation, and patients younger than 18 years of age were excluded from the study. The etiology of HF was considered ischemic in the presence of significant coronary artery disease (≥50% stenosis of one or more major coronary arteries) and/or a history of myocardial infarction or previous revascularization.

All patients underwent complete physical examination (6-minute walk test, electrocardiography, transthoracic echocardiography (TTE), 24-hour electrocardiogram (ECG) monitoring, coronary angiography, and blood tests), MPS with ^{99}mTc-MIBI, and RTVG before and 6 months after device implantation. In all cases, cardiac resynchronization therapy devices with cardioverter-defibrillator (CRT-D) function were implanted according to ESC guidelines [3]. All patients received baseline therapy in accordance with current recommendations. Follow-up was performed 6 months after implantation of CRT-D.

Agreement form

The study was conducted in accordance with the principles of the Declaration of Helsinki and standards of good clinical practice. The study was approved by the local ethical committee and was performed at a research institute. All participants obtained written informed consent prior to inclusion in the study.

The 6-minute walk test

The severity of HF was assessed using NYHA criteria, with the 6-minute walk test. Walking distance in meters and the NYHA FC to which it corresponded were used for analysis:

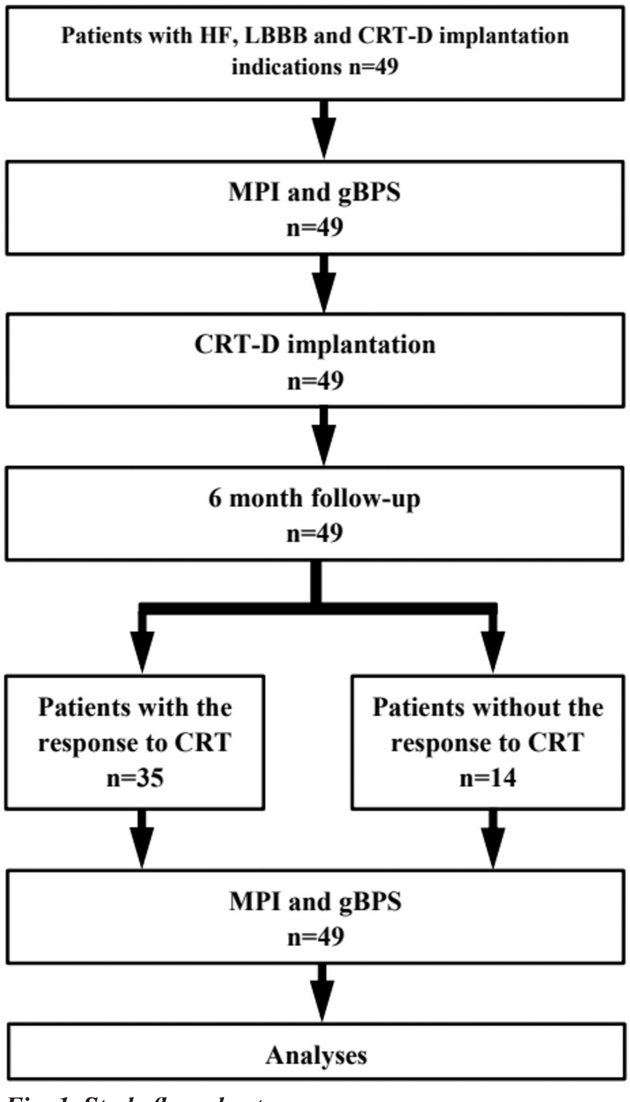

Fig. 1. Study flow chart.

- more than 551 m - the patient has no signs of HF;
- 426-550 m - belong to I FC;
- 301-425 m - belong to II FC;
- 151-300 m - belong to III FC;
- less than 150 m - belong to IV FC.

Transthoracic echo

Transthoracic echo with evaluation of intracardiac hemodynamic parameters was performed on a Philips HD15 PureWave ultrasonic diagnostic device (Netherlands) before and 6 months after implantation of CRT-D. The study was performed from standard Echo positions with determination of left atrium, right ventricle (RV) size, interventricular septum (IVS) thickness, LV posterior wall, LV end-systolic dimension (LVESD), LV end-diastolic dimension, LV end-systolic volume (LVESV), LV end-diastolic volume, myocardial mass index, LVEF, LV systolic pressure, stroke volume, end-systolic index, end-diastolic index, left atrial index, and right atrial index. Mitral, tricuspid, and aortic valve function, as well as LV and LV contractility were assessed.

Radionuclide imaging

Radionuclide studies were performed on a Discovery NM/CT 570c single-photon emission computed tomography scanner (GE Healthcare, Haifa, Israel) equipped with a gamma camera with semiconductor cadmium-zinc-tellurium detectors. Images were acquired in tomographic mode using a low-energy multi-pinhole collimator in 19 projections in a 32×32 pixel matrix. The center of the energy window was

Table 1.

Clinical and demographic characteristics of patients by groups

	Total (n=49)	Group 1 respondents (n=35)	Group 2 nonresponders (n=14)	P_{2-3}
	1	2	3	
Age, years, M±SD	58.3±11.4	57.9±10.2	59.1±14.5	0.911
Male gender, n (%)	34 (69.4)	24 (68.5)	10 (71.4)	0.885
Ischemic cardiomyopathy, n (%)	16 (32.6)	10 (28.5)	6 (42.8)	0.445
Non-ischemic cardiomyopathy, n (%)	33 (67.4)	25 (71.5)	8 (57.2)	0.445
6-minute walk test, m, M±SD	294.9±67.6	289.4±65.3	308.5±73.5	0.382
NYHA functional class of heart failure:				
II, n (%)	23 (46.9)	14 (40.0)	9 (64.3)	0.191
III, n (%)	26 (53.1)	21 (60.0)	5 (35.7)	0.191
Arrhythmias prior to implantation of a cardiac resynchronization therapy device with defibrillation function				
Persistent VT, n (%)	4 (8.1)	2 (5.7)	2 (14.3)	0.650
Unstable VT, n (%)	16 (32.6)	12 (34.3)	4 (28.6)	0.765
Atrial fibrillation, n (%)	14 (28.5)	9 (25.7)	5 (35.7)	0.595
Associated pathology				
Arterial hypertension, n (%)	16 (32.6)	11 (31.5)	5 (35.7)	0.623
LV myocardial hypertrophy, n (%)	40 (81.6)	27 (77.1)	13 (92.8)	0.400
Diabetes mellitus, n (%)	8 (16.3)	7 (20.0)	1 (7.1)	0.492
Body mass index, kg/m², M±SD	28.8±4.9	29.4±5.3	27.4±3.4	0.298
Dyslipidemia, n (%)	23 (46.9)	17 (48.5)	6 (42.8)	0.765
eGFR, ml/min/1.73 m², M±SD	74.3±19.8	77.5±19.3	66.0±19.1	0.101
Drug therapy				
Beta-adrenoblockers, n (%)	48 (97.9)	34 (97.1)	14 (100.0)	0.885
Loop diuretics, n (%)	31 (63.2)	18 (51.4)	13 (92.8)	0.025
Aldosterone antagonists, n (%)	35 (71.4)	28 (80.0)	7 (50.0)	0.106
ACEI, n (%)	22 (44.9)	14 (40.0)	8 (57.2)	0.353
Antiplatelets, n (%)	30 (61.2)	20 (57.1)	10 (71.4)	0.445
Statins, n (%)	35 (71.4)	28 (80.0)	7 (50.0)	0.106
Amiodarone, n (%)	17 (34.7)	11 (31.5)	6 (42.8)	0.542
Angiotensin receptor antagonists, n (%)	24 (48.9)	20 (57.1)	4 (28.6)	0.124
SGLT2 inhibitors, n (%)	8 (16.3)	7 (20.0)	1 (7.1)	0.492

Note: hereafter, M±SD values for quantitative variables and n (%) values for categorical variables; NYHA - New York Heart Association; VT - ventricular tachycardia; LV, left ventricle; eGFR estimated glomerular filtration rate; ACEI, angiotensin-converting enzyme inhibitors; SGLT2, sodium-glucose cotransporter type 2.

set to a ^{99m}Tc photopeak of 140 keV; the width of the energy window was symmetric and 20%. The obtained data were processed on a specialized workstation (Xeleris II; GE Healthcare, Haifa, Israel). MPS and RTVG were performed before and 6 months after implantation of CRT-D.

MPS was performed in the patient in the state of functional rest, 90 minutes after the injection of 370-450 MBq with ^{99m}Tc-MIBI. The study was performed in tomographic mode with ECG synchronization (16 frames per cardiac cycle). The duration of the recording was 6 minutes. Image reconstruction was performed along the short and long (horizontal and vertical) axes of the heart, as well as using a normalized 17-segment LV polar map. Semi-quantitative calculation of local LV perfusion abnormalities was performed as a percentage. Perfusion disturbance was calculated in points in each of 17 LV segments according to 5-point scale, where 0 - normal accumulation of radiopharmaceutical in myocardium, and 4 points - sharply expressed defects of indicator accumulation. The total percentage of perfusion impairment was defined as the ratio of the sum of scores in all 17 segments to the maximum possible perfusion impairment value of 68.

To perform RTVG, the patient was injected intravenously with 2 mL of Pirfotech solution. Then, intravenous injection of 555-720 MBq of ^{99m}Tc-pertechnetate was performed 10 minutes later. After 10 minutes, data were recorded on a gamma camera. The patient was positioned so that the center of the left ventricle of the heart was in the center of the detector field of view. Recordings were performed in ECG-synchronized mode, recording duration - 10 minutes. Postprocessing of the results included separation of the cavities of both ventricles of the heart with subsequent determination of their contours. Parameters characterizing the ventricular function of the heart were calculated from the dynamics of the count rate per cardiac cycle in the corresponding zone of interest. Phase characteristics were calculated from phase histograms obtained using the Fourier transform. Quantitative indices (phase standard deviation, phase histogram width and entropy) of global dyssynchrony were calculated and separately for each zone of interest: anterior, lateral posterior LV wall, IVS, and LV free wall.

Implantation and programming of CRT-D

Implantation of atrial and defibrillating electrodes with active fixation and left ventricular electrode (LVE) with passive fixation was performed under fluoroscopic control through transvenous access. The defibrillating electrode was implanted in the apex of the LV or IVS. Electrode positioning was performed under fluoroscopy in the anteroposterior and left lateral projections. Stimulation threshold, intracardiac signal amplitude and electrode impedance were measured using a cardiac stimulation system analyzer (Medtronic, USA) with sterile cables with clamps.

LVE implantation was performed by cannulation of one of the veins of the coronary sinus using a delivery system. Venogram was performed in anteroposterior and left lateral projections. Access to the target vein in the coronary sinus and subsequent advancement of the LVE was performed using a guidewire. A subselector was used if there was difficulty in catheterizing the target vein. LVE positioning in the target vein was performed after testing electrode thresholds and verifying diaphragmatic nerve stimulation.

Programming of CRT-D was carried out in accordance with international standards [19]. All patients were programmed for biventricular stimulation with optimal atrioventricular and interventricular (LV was stimulated before RV by 0-40 ms) delay. In each CRT-D, a monitoring zone was programmed with a heart rate of 140-170 beats

Table 2.

Postoperative parameters in groups of patients

	Total (n=49)	Group 1 respondents (n=35)	Group 2 nonresponders (n=14)	P_{2-3}
	1	2	3	
Position of the left ventricular electrode in the target vein				
Collateral vein, n (%)	20 (40.8)	17 (48.5)	3 (21.4)	0.144
Posterolateral vein, n (%)	15 (30.6)	9 (25.7)	6 (42.8)	0.358
Anterolateral vein, n (%)	9 (18.4)	8 (17.1)	3 (21.4)	0.824
Posterior vein, n (%)	5 (10.2)	3 (8.5)	2 (14.3)	0.765
Quadripolar left ventricular electrode, n (%)	28 (57.2)	24 (68.5)	4 (28.6)	0.030
Bipolar left ventricular electrode, n (%)	21 (42.8)	11 (31.5)	10 (71.4)	0.030
QRS complex duration				
Native QRS, ms, M±SD	171.0±15.6	172.3±15.7	168.0±15.5	0.394
Stimulated QRS, ms, M±SD	135.9±13.0	135.4±13.5	137.1±12.0	0.603
ΔQRS, ms, M±SD	35.1±14.2	36.8±12.9	30.8±16.9	0.180
Programmed delaysи				
Paced AV delay, ms, M±SD	153.8±15.6	154.0±15.0	153.5±17.8	0.773
Sensed AV delay, ms, M±SD	119.1±18.0	120.5±17.9	115.3±18.4	0.587
Interventricular delay, ms, Me [Q1, Q3]	30.0 [20.0; 40.0]	30.0 [20.0; 40.0]	20.0 [10.0; 40.0]	0.610

Note: hereafter AV is atrioventricular.

per minute (bpm) with more than 50 consecutive cycles without antitachycardia stimulation and shock discharge. Ventricular tachycardia (VT) zone was programmed at 170-200 beats/min with 30 cycles and with antitachycardia stimulation (≥1 «burst» stimulation and ≥1 «ramp» stimulation) and shock discharge (first discharge with submaximal magnitude). Ventricular fibrillation zone was programmed at 201-240 beats/min with 12 cycles and with antitachycardia stimulation during CRT-D shock charge recruitment and maximal shock discharge.

Follow-up

Information on arrhythmic events was determined by interview and CRT-D programming. Arrhythmic events (VT, ventricular fibrillation, atrial fibrillation, adequate and inadequate CRT-D therapy), percentage of biventricular stimulation, as well as indices (stimulation threshold, intracardiac signal amplitude and impedance) of CRT-D electrodes were evaluated. The block diagram of the study is presented in Fig. 1. The criteria for positive response after 6 months of follow-up were as follows: improvement in NYHA FC ≥1 class + decrease in LVESV >15% or improvement in NYHA FC ≥1 class + improvement in LVEF >5% [17].

Statistical analysis

Statistical analysis was performed using Statistica 10.0 program package, StatSoft (USA). The Shapiro-Wilk test was used to assess the normality of the trait distribution. The mean (M) and standard deviation (SD) were calculated for variables with normal distribution, and the median (Me) with interquartile range [Q1, Q3] was calculated for the others. Nonparametric Mann-Whitney test for independent samples and Wilcoxon test for dependent samples were used. Spearman's nonparametric analysis was used to assess correlations and collinearity between pairs of quantitative traits. Efficiency analysis was performed using logistic regression analysis. Stepwise logistic regression analysis was used to assess independent predictors of response to CRT. ROC analysis was used to determine the diagnostic efficiency of the method using the MedCalc statistical software package. At the significance level p less than 0.05, it was considered that the studied indicator in the compared groups had statistically significant differences.

RESULTS

Patient characteristics

A total of 49 (100.0%) patients who underwent MPS and RTVG before and 6 months after implantation of CRT-D were included in the study. The first group consisted of 35 (71.4%) patients with a positive response to CRT (responders), and the second group consisted of 14 (28.6%) patients without a positive response to CRT (nonresponders). Baseline demographic and clinical characteristics of the included patients are presented in Table 1. The mean age of the patients was 58.3±11.4 years, 34 (69.4%) were male. Baseline 6-minute walk test, NYHA CHF, QRS complex duration, arrhythmias recorded before CRT-D implantation, LVE position, CHF etiology, concomitant pathology, and drug treatment of patients in the groups are also shown in the Table 1. The groups did not differ sig-

Table 3.

Main indices of intracardiac hemodynamics according to echocardiography results

	Group 1 respondents (n=35)			Group 2 nonresponders (n=14)			P_{1-4}	P_{2-5}
	Initially	After 6 months	P	Initially	After 6 months	P		
	1	2	3	4	5	6		
LVESV, ml	162.0 [130.0; 200.0]	112.0 [93.0; 142.0]	<0.001	197.5 [151.0; 263.0]	195.0 [132.0; 265.0]	0.694	0.106	<0.001
LVEF, %	30.0 [25.0; 33.0]	38.0 [35.0; 44.0]	<0.001	27.0 [22.0; 31.0]	28.5 [25.0; 30.0]	0.059	0.358	<0.001
MMI, g/m^2	135.0 [118.0; 150.0]	112.0 [99.0; 136.0]	0.004	150.5 [130.0; 166.0]	144.0 [125.0; 194.0]	0.463	0.116	0.002
LVEF, ml	234.0 [198.0; 263.0]	188.0 [148.0; 220.0]	<0.001	266.0 [216.0; 341.0]	266.0 [200.0; 351.0]	0.916	0.207	0.003
LAI, ml/m^2	53.3 [45.0; 65.2]	46.2 [35.2; 53.0]	<0.001	60.9 [48.5; 72.1]	67.4 [44.7; 76.5]	0.386	0.199	0.009
RAI, ml/m^2	32.7 [27.7; 48.4]	32.2 [28.1; 42.6]	0.075	44.5 [31.3; 56.4]	46.4 [34.7; 62.0]	0.332	0.240	0.014
EDI, ml/m^2	118.6 [99.8; 141.1]	95.4 [74.4; 116.2]	<0.001	127.9 [117.4; 152.9]	132.4 [106.7; 177.1]	0.593	0.126	<0.001
ESI, ml/m^2	85.0 [68.6; 97.7]	56.0 [47.6; 76.7]	<0.001	92.6 [82.6; 122.4]	98.2 [70.4; 132.7]	0.396	0.090	<0.001
RVSP, mm Hg	30.0 [25.0; 41.0]	29.0 [26.0; 35.0]	0.154	33.5 [25.0; 46.0]	37.5 [27.0; 47.0]	0.123	0.406	0.050
LVSI	0.66 [0.60; 0.72]	0.61 [0.57; 0.65]	<0.001	0.69 [0.67; 0.72]	0.68 [0.63; 0.71]	0.875	0.268	0.001

Note: LVESV - end-systolic volume, LVEF - LV ejection fraction, MMI - myocardial mass index, LVEDV - left ventricular end-diastolic volume, LAI - left atrial index, RAI - right atrial index, EDI - end-diastolic index, ESI - end-systolic index, RVSP - right ventricular systolic pressure, LVSI - left ventricular sphericity index.

nificantly in baseline clinical and demographic variables, except for loop diuretics administration. There were significantly more patients taking loop diuretics in the second group than in the first group (p=0.025).

All patients were implanted with CRT-D. Postoperative parameters are presented in Table 2. The groups did not differ significantly in terms of postoperative parameters except for the following: implanted quadripolar and bipolar LVEs. There were significantly more patients in the second group of patients who were implanted with bipolar LVE than in the first group (p=0.03, respectively). In the first group, the number of patients who were implanted with quadripolar LVEs was significantly higher than in the second group (p=0.03). Given that multipole stimulation was not used in this study and that there were no differences between the groups in stimulated QRS complex duration, atrioventricular and interventricular delay, such heterogeneity in the number of implanted quadripolar LVEs did not significantly affect the positive response to CRT.

Echo was performed in all patients before and 6 months after implantation of CRT-D. The main parameters of echocardiography with assessment of intracardiac hemodynamics are presented in Table 3. The groups were comparable in terms of the main indices of intracardiac hemodynamics assessed by transthoracic echo before CRT-D implantation. At 6 months after implantation of CRT-D in the group of responders there was a significant improvement of all parameters, except for the right atrial index and right ventricular systolic pressure. No improvement was found in the non-responders group 6 months after CRT-D implantation.

In addition to basic diagnostic methods, all patients underwent resting MPS and RTVG. The main indicators of radionuclide diagnostics are presented in Table 4. The groups were comparable in terms of baseline resting

Table 4.

Main indices of myocardial perfusion scintigraphy and radionuclide tomoventriculography

	Group 1 respondents (n=35)			Group 2 nonresponders (n=14)			P_{1-4}	P_{2-5}
	Initially	After 6 months	P	Initially	After 6 months	P		
	1	2	3	4	5	6		
InterVD, ms	93.0 [48.0;123.0]	53.0 [37.0;72.0]	0.004	31.4 [20.0;42.3]	60.8 [20.0;42.3]	0.050	<0.001	0.748
IntraVD LV, ms	137.0 [105.0;181.0]	91.0 [56.0;123.0]	<0.001	132.4 [96.7;153.0]	105.3 [90.7;119.4]	0.020	0.499	0.313
IntraVD RV, ms	104.0 [66.6;149.1]	90.0 [56.4;115.0]	0.019	89.9 [54.7;132.0]	82.6 [45.0;161.0]	0.952	0.465	0.947
LV wall entropy:								
LV, %	72.0 [66.0;82.0]	70.0 [62.0;76.0]	0.186	66.0 [52.0;72.0]	71.0 [63.0;81.0]	0.278	0.032	0.790
SW, %	68.0 [57.0;79.0]	53.0 [42.0;65.0]	<0.001	56.0 [50.0;65.0]	57.0 [44.0;70.0]	0.484	0.184	0.438
AW, %	52.0 [45.0;62.0]	49.0 [39.0;55.0]	0.016	37.5 [30.0;50.0]	48.5 [39.0;57.0]	0.109	<0.001	0.991
LW, %.	37.0 [31.0;49.0]	46.0 [35.0;54.0]	0.092	36.0 [30.0;50.0]	49.5 [32.0;58.0]	0.015	0.506	0.690
IW, %	58.0 [49.0;63.0]	52.0 [42.0;65.0]	0.467	59.5 [58.0;64.0]	62.5 [54.0;72.0]	0.552	0.207	0.031
PSD LV wall:								
SW, °	40.0 [27.0;60.0]	24.0 [14.0;30.0]	<0.001	23.0 [15.0;35.0]	23.5 [16.0;37.0]	0.593	0.024	0.412
AW, °	25.0 [17.0;34.0]	18.0 [11.0;24.0]	0.008	10.0 [9.0;24.0]	21.5 [15.0;32.0]	0.008	<0.001	0.259
LW, °	12.0 [8.0;25.0]	14.0 [9.0;21.0]	0.411	12.0 [7.0;20.0]	27.5 [8.0;47.0]	0.034	0.690	0.173
IW, °	26.0 [17.0;39.0]	19.0 [11.0;30.0]	0.317	28.0 [25.0;43.0]	35.5 [24.0;50.0]	0.888	0.156	0.004
SRS, %	5.0 [3.0;11.0]	5.0 [3.0;8.0]	0.308	8.5 [4.0;13.0]	12.0 [4.0;13.0]	0.132	0.513	0.004
HBW LV, °	212.0 [175.0;234.0]	195.2 [175.0;241.0]	0.805	199.0 [192.0;211.0]	201.0 [208.3;213.1]	0.278	0.535	0.090

Note: LVHBW - left ventricular histogram bandwidth, PSD - standard deviation of phase histogram, SRS - resting radiopharmaceutical filling defect, LW - lateral wall, IntraVD - intraventricular dyssynchrony, LV - left ventricle, InterVD - interventricular dyssynchrony, IW - inferior wall, RV - right ventricle, SW - septal wall, AW - anterior wall.

MPS and RTVG before CRT-D implantation, except for interventricular dyssynchrony (InterVD) (p<0.001), LV entropy (p=0.032), LV anterior wall entropy (p<0.001) and LV septal phase histogram standard deviation (PSD) (p<0.001). 6 months after implantation of CRT-D in the group of responders there was a significant improvement in the following indices of LV mechanical dyssynchrony: InterVD, intraventricular LV and LV dyssynchrony, entropy and PSD of the septum and LV anterior wall (Table 4). In the nonresponders group, there was a significant improvement in LV intraventricular dyssynchrony, worsening of entropy and PSD of the LV lateral wall, and PSD of the LV anterior wall (AWLV).

Arrhythmic events according to CRT-D data

During 6 months of follow-up, episodes of VT as measured by the CRT-D questionnaire were reported in 9 (18.3%) patients in both groups. In the group of responders, VT was registered in 5 (14.3%) patients: 4 patients had unstable VT (self-corrected) and 1 patient had stable VT, treated with CRT-D shock. In the group of nonresponders, VT was registered in 4 (28.5%) patients (p=0.445). In this group, all 4 patients had an unstable VT. Shock triggers in the nonresponders group have not been documented. No dysfunction of the CRT-D-electrode system, electrode dislocations, or unwarranted CRT-D therapy was observed in either group. The percentage of biventricular stimulation 6 months after CRT-D implantation was 97.8±2.6% in the responder group and 98.4±0.9% in the nonresponder group. During 6 months of follow-up, paroxysms of atrial fibrillation were recorded by CRT-D in 2 patients from both groups, 1 in the responder group and 1 in the nonresponder group (p=0.706). Atrial fibrillation in these patients resolved on its own.

Predictors of CRT responsiveness

Logistic regression analysis as a method of mathematical modeling allows not only to identify predictors of events, but also to build a predictive model that considers several parameters. Considering the impossibility of including in one prognostic model the factors between which there is a statistical relationship, before creating a mathematical model including more than one predictor, we tested the prognostic factors for collinearity - we identified correlations and associations between the factors. According to the results of correlation analysis, the following parameters were excluded from the prognostic model: ΔQRS (correlates with QRS [r=0.611; p<0.001]), Δ6-minute walk test (correlates with ΔInterVD [r=-0.449; p=0.001]), Δ LVESV (correlates with PSD [r=0.437; p=0.001]) and entropy [r=0.419; p=0.001] of AWLV), ΔLVEF (correlates with Δ6-minute walk test [r=0.662; p<0.001], ΔLVESV [r=-0.674; p<0.001] and standard deviation of left ventricular anterior wall phase histogram (PSD of AWLV) [r=-0.511; p<0.001]), InterVD (correlates with ΔInterVD [r=0.718; p<0.001]), LV entropy (correlates with entropy [r=0.617; p<0.001] and PSD [r=0.500; p<0.001] of AWLV), PSD of LV septum (correlates with PSD of AWLV [r=0.558; p<0.001]), ΔPSD of AWLV (correlates with PSD of LV PSD [r=0.668; p<0.001]) and entropy of AWLV (correlates with PSD of AWLV [r=0.854; p<0.001]).

According to the collinearity results, commonly known predictors of positive response to CRT (QRS complex duration, female sex, and non-ischemic cardiomyopathy) and indices with significant differences between groups (ΔInterVD, ΔPSD of LV septum and anterior wall, and Δentropy of AWLV) were included in multivariate logistic regression analysis. This analysis showed that only ΔInterVD (odds ratio [OR] 1.0349; 95% confidence interval [CI] 1.0075-1.0631; p=0.01) and PSD of AWLV (OR 1.1693; 95% CI 1.0502-1.3020; p=0.004) were independently associated with a positive response to CRT. An increase in the prognostic coefficient calculated using ΔInterVD and PSD of the LV anterior wall greater than 0.67 was a predictor of a positive response to CRT (area under the curve 0.918; sensitivity 85.71; specificity 85.71; p<0.001) (Figure 2). Pairwise comparison of the ROC curve of PC of positive response to CRT with ΔInterVD and PSD of AWLV showed significant differences with ΔInterVD (p=0.009) (Figure 3).

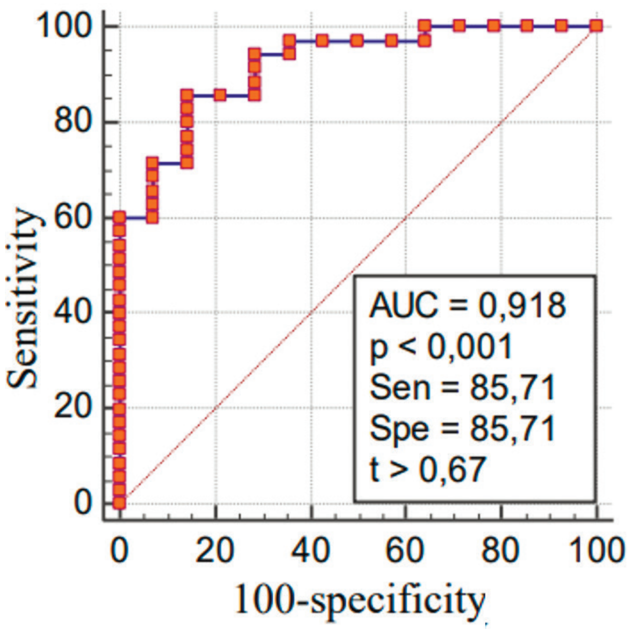

Fig. 2. CRT response probability indicator, calculated according to the predictive model. Notes: AUC - area under curve, Sen - sensitivity, Spe - specificity, t - threshold value.

DISCUSSION

The present study shows that mechanical dyssynchrony (standard deviation of left ventricular anterior wall phase histogram and Δ interventricular dyssynchrony), as measured by MPS and RTVG in patients with CHF and LBBB, may have prognostic value. Thus, PSD of AWLV and ΔInterVD are prognostic indicators of a positive response to CRT. This may be due to marked interventricular delay and involvement of the LV anterior wall in mechanical dyssynchrony.

It has been previously reported that nonischemic cardiomyopathy is a predictor of reverse LV myocardial remodeling in patients with CHF. According to C.Ypenburg et al (2009) CRT responders and super responders were more likely to have a non-ischemic etiology of CHF [20]. In a study by D.Verhaert et al (2010), female gender and non-ischemic cardiomyopathy were shown to be associated with a positive response to CRT in the early period after CRT device implantation [21]. Another study by F.Said et al (2021) showed that female subjects were more likely to have a greater positive echocardiographic response to CRT after 6 months of follow-up [22]. However, after adjusting for body surface area and ischemic etiology, no differences in LV function and survival were found, suggesting that the non-ischemic etiology of CHF is responsible for the higher rates of positive response in women receiving CRT [22]. In our study, the number of patients with ischemic and non-ischemic cardiomyopathies in the groups with and without a positive response to CRT was not significantly different (p=0.445). Among others, multivariate logistic regression showed that nonischemic cardiomyopathy was not a predictor of positive response to CRT. This is probably due to the small sample size, which may affect the results.

The prognostic value of LV mechanical dyssynchrony assessed by MPS and RTVG for patient selection for CRT has been extensively studied. In a study involving 142 patients with CRT, MD LV parameters such as phase histogram width during systole (95% CI 0.98-1.00, p=0.041) and diastole (95% CI 0.98-1.00, p=0.028), phase deviation of histogram during diastole (95% CI 0.94-1.00, p=0.041) were significant independent predictors of CRT response only in patients with non-ischemic cardiomyopathy [16]. For individuals with ischemic cardiomyopathy, all parameters of LV mechanical dyssynchrony were not significant [16]. In a study by M.Henneman et al (2007) ROC analysis showed that the optimal threshold value of PSD and phase histogram width were 43° (sensitivity and specificity 74%) and 135° (sensitivity and specificity 70%), respectively [23]. In a study involving 324 patients with non-ischemic cardiomyopathy and an CRT device, it was shown that PSD adjusted for age, hypertension, diabetes, aspirin intake, beta-blocker, diuretic, QRS duration and LVEF was an independent predictor of all-cause mortality (OR 1.97, 95% CI 1.06-3.66, p=0.033) [24].

In our study, responders and nonresponders did not differ in measures of global LV mechanical dyssynchrony such as phase histogram width, and this index had no prognostic value, but PSD and InterVD were higher in the responders' sample. However, the novelty of our study was the use of RTVG to assess regional mechanical dyssynchrony separately for the septum, anterior, posterior, and lateral LV walls. These parameters were statistically significant predictors of response to CRT. Multivariate logistic regression showed that ΔInterVD (OR 1.0349; 95% CI 1.0075-1.0631; p=0.01) and PSD of AWLV (OR 1.1693; 95% CI 1.0502-1.3020; p=0.004) were independently associated with a positive response to CRT. This may suggest that assessment of regional myocardial dyssynchrony may provide additional information for successful resynchronization therapy. But disagreements with previous studies emphasize the importance of these results and the need for future large-scale studies.

Few publications on the combined assessment of factors associated with reverse myocardial remodeling that can be used to improve patient selection for CRT are found in the available literature. The value of assessing response to CRT was shown in the large randomized MADIT-CRT trial [18]. According to this study, a multivariate analysis including seven factors associated with echocardiographic response to CRT-D (female sex, nonischemic cardiomyopathy, LBBB, QRS complex duration ≥150 ms, prior hospitalization for CHF, LV end-diastolic volume index ≥125 ml/m^2 and left atrial volume index <40 ml/m^2) showed a significant reduction in the risk of CHF or death in subgroups of up to 69% (p<0.001).

In our study, multivariate logistic regression, which included such commonly occurring factors as QRS complex duration, female sex, non-ischemic cardiomyopathy, and indices of mechanical dyssynchrony with significant differences between groups (ΔInterVD, ΔPSD of LV septum and anterior wall, Δentropy of LV AV) showed that ΔInterVD (OR 1.0349; 95% CI 1.0075-1.0631; p=0.01) and PSD of AWLV (OR 1.1693; 95% CI 1.0502-1.3020; p=0.004) were independent predictors of positive response to CRT. An increase in the prognostic coefficient calculated using ΔInterVD and PSD of the LV anterior wall greater than 0.67 was a predictor of a positive response to CRT (area under the curve 0.918; sensitivity 85.71; specificity 85.71; p<0.001).

Thus, the prognostic model with the combination of PSD of AWLV and ΔInterVD has a high prognostic value and can be used as an additional predictor of positive response of CRT in patients with CHF.

Limitations of the study

Limitations of the study include the relatively small sample size, short follow-up period, and the fact that it was non-randomized and single-center, which could ultimately affect the final results.

CONCLUSION

Mechanical dyssynchrony assessed by MPS and RTVG is associated with a positive response to CRT in patients with CHF and LBBB. According to our prognostic model, a combined score of factors associated with reverse myocardial remodeling (PSD of AWLV and ΔInterVD) and an increase in PC greater than 0.67 is a predictor of a positive response to CRT.

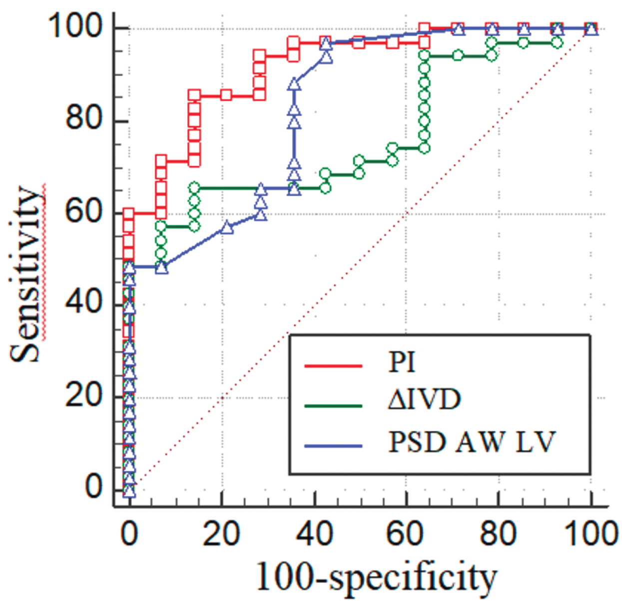

Fig. 3. Comparison of ROC curves of PI with the response to CRT. Notes: PI - probability indicator; ΔIVD - interventricular dyssynchrony; PSD AW LV - phase standard deviation anterior wall left ventricle.

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