Long Term Left Ventricular Reverse Remodeling and Functional Outcome after Cardiac Resynchronization in Advanced Heart Failure

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Abstract

Objectives: The purpose of this study was to assess long-term outcomes of cardiac resynchronization therapy (CRT) on left ventricular reverse remodeling and functional recovery in patients with advanced heart failure and to establish predictors for positive response to cardiac resynchronization.

Methods: The study population consisted of 48 patients (age 68 ± 8.51 years, 79.55% male). Patients underwent transthoracic echocardiography, electrocardiogram, the 6-minute walk test (6MWT) and NYHA functional class evaluation before biventricular pacemaker implantation and during follow-up.

Results: Median follow-up was 21.89 ± 9.21 months. 4 (7.7%) patients died from heart failure. Reverse left ventricular remodeling was observed in 77.08% (N=37) patients. CRT resulted in statistically significant improvement of NYHA functional class (p=0.015) and the increased results of 6MWT (p=0.000). Logistic regression analysis demonstrated lower pulmonary artery systolic pressure (PASP) (OR 1.152, 95% CI 1.026-1.293; p=0.017) and more severe mitral regurgitation (OR 0.11, 95% CI 0.018-0.769; p=0.025) prior to device implantation as significant predictors of positive response to CRT. Poor response cut-off value of PASP ≥ 46 mmHg was established in ROC analyses, with 78% of sensitivity and 62% of specificity.

Conclusions: Our study confirmed the reversible cardiac remodeling and improvement in systolic left and right ventricular function and functional condition in advanced heart failure patients treated with CRT. According to our study, lower pulmonary artery pressure and more severe mitral regurgitation prior to device implantation predicted favorable long-term response to CRT.

Keywords: Cardiac resynchronization therapy; Chronic heart failure; CRT responder; Reverse remodeling

Introduction

The guidelines for chronic heart failure recommend cardiac resynchronization therapy (CRT) as a class I indication, level A evidence, for clinical patients' outcomes improvement. Traditionally several types of indices are used to assess response to CRT: clinical, functional, electrical, echocardiographic, hemodynamic, neuro-hormonal [1-7].

Despite various studies ascertainment that CRT is efficient for the majority of patients, there are a significant proportion of non-responders. The literature review demonstrates different criteria of positive response to CRT in clinical trials and rate of non-responders varies from 20% to 40%.

Accuracy of echocardiographic, electrical, clinical and functional parameters to predict response to CRT remains controversial [8-12].

The purpose of this study is to assess long-term outcomes of CRT on left ventricular reverse remodelling and functional recovery in patients with advanced heart failure and to establish predictors for positive response to cardiac resynchronization therapy.

Materials and Methods

The study population consisted of 48 patients (age 68.0 ± 8.5 years, 79.5% male) who were treated with CRT-P at the Hospital of Lithuanian University of Health Sciences from 2014/01/01 to 2016/10/31 and met the standard indications for this therapy: New York Heart Association (NYHA) functional class II-IV (ambulatory), LVEF of 35.0% or less, prolonged QRS interval more than 120.0 ms and on optimal medical therapy.

The study protocol was approved by the local ethics committee and all subjects provided written informed consent. According to study protocol patients underwent transthoracic 2-dimentional echocardiography (TTE), surface electrocardiogram (ECG), the 6-minute walk test (6MWT) and NYHA functional class evaluation before biventricular pacemaker implantation and during follow-up.

According to the response to CRT, patients were classified as responder or non-responder. The response was considered as positive, if left ventricular end-systolic volume index decreased more than 10.0% during the observation period. The lack of reduction of left ventricular end-systolic index and/or death from heart failure was considered as non-response to CRT.

Depending on primary disease, patients were classified as "ischemic" or "non-ischemic". Those, who have had myocardial

infarction, angina and coronary artery stenosis more than 75.0 %, were considered as "ischemic".

Echocardiographic characteristics including left ventricular end-diastolic diameter and index (LVEDD, LVEDDi), left ventricular end-systolic and end-diastolic volumes and indices (LVESV, LVESVi, LVEDV, LVEDVi), left ventricular ejection fraction (LVEF), grade of left ventricular diastolic dysfunction, left atrial diameter, volume and index (LA, LAV, LAVi), grade of mitral valve regurgitation (MVR), right atrial and right ventricular diameters (RA, RV), tricuspid annular peak systolic excursion (TAPSE), velocity of the tricuspid annular systolic motion (RV S'), pulmonary artery systolic pressure (PASP) were analysed.

Statistical analysis was performed using "Statistical Package of Social Sciences" (SPSS 22.0) and "Microsoft Excel 2010" software. There were defined statistical characteristics, such as total observation number, mean, median and standard deviation by using descriptive statistics. Wilcoxon signed-rank test (for quantitative variables) and McNemar's tests (for qualitative variables) were used to evaluate changeability and statistical reliability of statistical data. Spearman's correlation coefficient (rs) was applied to measure the strength and direction of association between two ranked variables. Chi-square (for qualitative variables) and Mann-Whitney U non-parametric tests (for quantitative variables) were used to assess the relationship between the observation in each group and before and after treatment. Variables with a p value <0.05 were considered statistically significant. Receiver operating characteristic (ROC) curve was used to determine a cut-off point of categorical predictors. Variables significant in univariate analysis were added to logistic regression to determine independent predictors of response to CRT. Precision of the model was verified with the Hosmer-Lemeshow test of goodness of fit test.

Results

Median follow-up was 21.9 ± 9.2 months. 4 (7.7%) patients died from heart failure during observation period. The improvement of left ventricular function echocardiographic characteristics during follow-up was observed in study population: the average LVEF increased, LVEDD, LVEDDi, left ventricular volumes and their indices reduced. MVR grade diminished, moderate or severe MVR was established in 4 pts (9.1%) at follow-up *vs* 17 pts (35.4%) prior to device implantation (p=0.007).

The reduction of PASP and increase of TAPSE and RVS revealed the right ventricular function amelioration. Changes of echocardiographic parameters are shown in Table 1.

Parameter	Pre-CRT (N=48)	Post-CRT (N=44)	p-value
LVEF (%)	23.0 ± 8.2	33.6 ± 10.8	0
LVEDD (mm)	62.9 ± 6.5	59.5 ± 8.2	0
LVEDDi (mm/m^2)	32.1 ± 5.0	30.2 ± 5.6	0.001
LVESV (ml)	133.7 ± 47.3	104.3 ± 68.6	0
LVESVi (ml/m^2)	68.2 ± 24.9	53.0 ± 35.2	0
LVEDV (ml)	172.0 ± 45.4	151.5 ± 75.1	0.018
LVEDVi (ml/m^2)	87.7 ± 24.3	76.7 ± 38.2	0.016
LA (mm)	48.0 ± 5.9	48.0 ± 6.1	>0.05
LAV (ml)	95.9 ± 28.3	107.3 ± 44.4	>0.05
LAVi (ml/m^2)	48.6 ± 14.5	54.0 ± 21.3	>0.05
PASP (mmHg)	42.9 ± 13.0	34.0 ± 12.2	0
TAPSE (mm)	15.6 ± 3.2	19.0 ± 4.5	0
RV S'(cm/s)	9.2 ± 3.3	10.6 ± 2.5	0
RV (mm)	36.0 ± 4.8	38.2 ± 6.5	0.02
RA (mm)	47.0 ± 6.1	47.3 ± 7.2	>0.05

Table 1: Changes of echocardiographic parameters (LVEF: left ventricular ejection fraction; LVEDD: left ventricular end-diastolic diameter; LVEDDi: left ventricular end-diastolic diameter index; LVESV: left ventricular end-systolic volume; LVESVi: left ventricular end-systolic volume index; LVEDV: left ventricular end-diastolic volume; LVEDVi: left ventricular end-diastolic volume index; LA: left atrial diameter; LAV: left atrial volume; LAVi: left atrial volume index; PASP: pulmonary artery systolic pressure; TAPSE: tricuspid annular plane systolic excursion; RVS: velocity of the tricuspid annular systolic motion; RV: right ventricular diameter; RA: right atrial diameter; pre-CRT: before device implantation; post-CRT: follow up after device implantation).

The significant reduction in left ventricular electrical dyssynchrony comparing follow-up QRS complex duration with prior to device implantation was observed: QRS complex narrowed from 178.7 ± 21.7 ms to 135.3 ± 16.2 ms (p=0.000).

Significant weak correlation between QRS complex duration and left ventricular function echocardiographic characteristics was revealed: LVEF rs=0.40, LVESV rs=0.35, LVESVi rs=0.36, LVEDV rs=0.30, LVEDVi rs=0.31.

Functional parameters, which are representative of the patient's clinical outcome, were evaluated. CRT resulted in statistically significant improvement of NYHA functional class and the increased results of 6MWT (Table 2).

Parameter	Pre-CRT (N=48)	Post-CRT (N=44)	p-value
	I-0.0% (N=0)	I-18.2% (N=8)	0.015
	II-8.3% (N=4)	II-59.1% (N=26)	
	III-66.7% (N=32)	III-18.2% (N=8)	
NYHA functional class	IV-25.0% (N=12)	IV-4.5% (N=2)	
6MWT (m)	232.7 ± 69.7	360.2 ± 83.3	0

Table 2: Changes of functional parameters in study population (6MWT: 6 minute walk test; pre-CRT: before device implantation; post-CRT: follow up after device implantation).

Reverse left ventricular remodeling was observed in 77.1% (N=37) patients. According to response to CRT, there was not a statistical significant difference of distribution by mean age (67.5 ± 9.0 *vs* 71.1 ± 9.1 years, p>0.05) and follow-up duration (19.4 ± 9.1 *vs* 22.3 ± 7.3 months, p>0.05) between responder and non-responder groups. All non-responder group patients were male.

Responders to CRT differed from non-responders by the lower level of pulmonary hypertension and better right ventricular function prior to device implantation (Table 3).

Parameter		Responder (N=37) Mean ± SD	p-value	Non-responder (N=11) Mean ± SD	p-value	p-value
LVEF (%)	Pre-CRT	23.4 ± 8.2		22.8 ± 7.3		0.838
	Post-CRT	35.5 ± 10.0	0.000	23.7 ± 9.6	0.588	0.016
LVEDD (mm)	Pre-CRT	62.1 ± 6.2		62.1 ± 8.9		0.997
	Post-CRT	57.4 ± 6.6	0.000	70.6 ± 7.0	0.024	0.002
LVEDDi (mm/m^2)	Pre-CRT	32.0 ± 4.7		29.9 ± 6.4		0.321
	Post-CRT	29.4 ± 5.1	0.000	34.2 ± 7.0	0.001	0.125
LVESV (ml)	Pre-CRT	129.9 ± 48.5		137.6 ± 39.1		0.596
	Post-CRT	85.2 ± 46.9	0.000	205.1 ± 80.0	0.001	0.007
LVESVi (ml/m^2)	Pre-CRT	66.8 ± 25.0		66.9 ± 23.3		0.991
	Post-CRT	43.8 ± 23.4	0.000	101.6 ± 48.1	0.000	0.018
LVEDV (ml)	Pre-CRT	167.7 ± 46.6		178.4 ± 41.4		0.478
	Post-CRT	129.2 ± 49.4	0.000	269.4 ± 80.6	0.000	0.003
LVEDVi (ml/m^2)	Pre-CRT	86.3 ± 24.1		86.2 ± 24.9		0.997
	Post-CRT	66.3 ± 24.8	0.000	131.8 ± 50.4	0.000	0.013
LA (mm)	Pre-CRT	47.4 ± 5.9		49.9 ± 4.7		0.151
	Post-CRT	46.9 ± 6.0	0.546	53.9 ± 2.3	0.16	0
LAV (ml)	Pre-CRT	93.0 ± 26.4		927 ± 38.5		0.984
	Post-CRT	101.0 ± 43.6	0.226	140.7 ± 34.1	0.053	0.022
LAVi (ml/m^2)	Pre-CRT	44.5 ± 12.9		44.8 ± 21.8		0.701
	Post-CRT	51.5 ± 20.9	0.145	67.7 ± 18.8	0.065	0.07
PASP (mmHg)	Pre-CRT	42.0 ± 12.2		53.8 ± 10.2		0.006
	Post-CRT	32.6 ± 11.0	0.003	42.3 ± 16.0	0.001	0.005
TAPSE (mm)	Pre-CRT	15.7 ± 3.2		12.9 ± 3.7		0.035
	Post-CRT	19.2 ± 4.1	0.026	17.9 ± 6.6	0.045	0.636
RV S' (cm/s)	Pre-CRT	9.4 ± 3.5		8.2 ± 1.0		0.061
	Post-CRT	10.8 ± 2.4	0.019	9.7 ± 3.0	0.013	0.372
RV (mm)	Pre-CRT	38.4 ± 6.6		38.8 ± 6.2		0.85
	Post-CRT	37.3 ± 6.6	0.187	43.1 ± 3.3	0.011	0.003
RA (mm)	Pre-CRT	46.1 ± 5.6		49.2 ± 7.4		0.218
	Post-CRT	46.2 ± 6.9	0.906	53.3 ± 5.6	0.024	0.014

Table 3: Comparison of responders and non-responders echocardiographic parameters before device implantation and at follow-up (LVEF: left ventricular ejection fraction; LVEDD: left ventricular end-diastolic diameter; LVEDDi: left ventricular end-diastolic diameter index; LVESV: left

ventricular end-systolic volume; LVESVi: left ventricular end-systolic volume index; LVEDV: left ventricular end-diastolic volume; LVEDVi: left ventricular end-diastolic volume index; LA: left atrial diameter; LAV: left atrial volume; LAVi: left atrial volume index; PASP: pulmonary artery systolic pressure; TAPSE: tricuspid annular plane systolic excursion; RVS: velocity of the tricuspid annular systolic motion; RV: right ventricular diameter; RA: right atrial diameter; pre-CRT: before device implantation; post-CRT: follow up after device implantation).

Less prominent electrical dyssynchrony was observed in responders group at follow-up (p<0.05). QRS duration in responder group narrowed from 175.8 ± 20.4 ms to 132.5 ± 14.3 ms (p<0.005), in non-responder from 187.3 ± 24.4 ms to 150.0 ± 18.9 ms (p<0.005).

Significant difference in NYHA functional class distribution of responder and non-responder groups was detected at follow-up, responder's functional condition became better than non-responder. There was 83.8% (31/37) of NYHA I-II functional class patients in responder group and 42.9% (3/7) in non-responder at follow-up (p=0.005).

Analysis of echocardiographic parameters at follow-up revealed reduction in left ventricular size, volumes and their indices, better left ventricular systolic and diastolic function, lower degree of mitral regurgitation and lower pulmonary artery systolic pressure in responders group and further progress of left ventricular remodelling and right heart chambers dilatation in non-responders group (Table 3).

The redistribution of left ventricular diastolic dysfunction grade at follow-up is demonstrated in Figure 1.
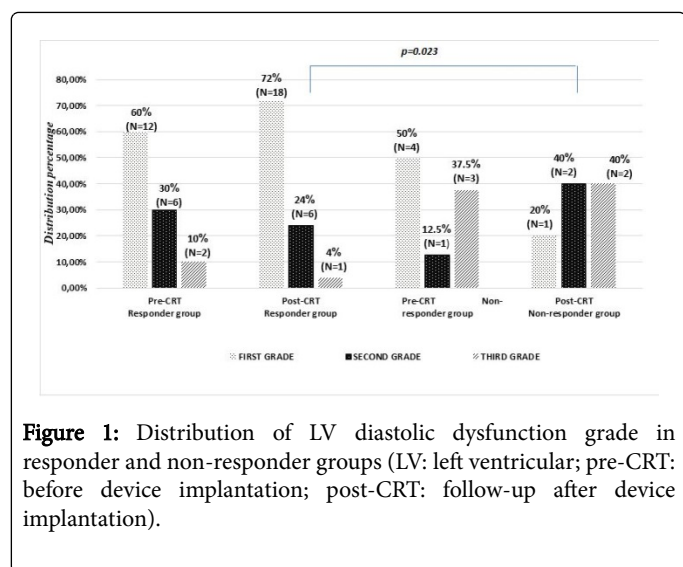
Figure 1: Distribution of LV diastolic dysfunction grade in responder and non-responder groups (LV: left ventricular; pre-CRT: before device implantation; post-CRT: follow-up after device implantation).

The reduction of MVR grade was observed in responder group at follow-up. Moderate or severe MVR was established in 15 pts (40.5%) prior to device implantation and in 2 pts (5.4%) at follow-up period (p=0.001). There wasn't any dynamics of MVR in non-responder group.

According to primary disease, 64.6% (N=31) patients were considered as "ischemic", while 35.4% (N=17) patients "non-ischemic". "Non-ischemic" patients were younger; their PASP was lower and left atrial volume bigger in comparison with "ischemic" patients before device implantation. During follow-up decrease of PASP in both groups patients was observed and difference between groups disappeared. Left atrial volume didn't changed in "non-ischemic" patients group at follow-up, but increased in "ischemic" and exceeds the LAV in "non-ischemic" patients. There were no differences

between other analysed parameters according to primary disease. Table 4 summarizes statistically significant differences between "ischemic" and "non-ischemic" patients.

Parameter		Ischemic N =31		Non-ischemic N =17		p-value
		Mean ± SD	p-value	Mean ± SD	p-value	
Age (years)		70.8 ± 9.5	-	63.9 ± 6.2	-	0.004
PASP (mmHg)	Pre-CRT	45.7 ± 13.9	0.002	39.7 ± 10.6	0.005	0.019
	Post-CRT	34.7 ± 13.1		32.7 ± 10.7		0.582
LAV (ml)	Pre-CRT	88.7 ± 31.8	0.032	102.8 ± 20.1	0.145	0.07
	Post-CRT	111.1 ± 53.5		100.8 ± 20.7		0.04

Table 4: Differences between "ischemic" and "non-ischemic" patients before device implantation and at follow-up (PASP: pulmonary artery systolic pressure; LAV: left atrial volume; pre-CRT: before device implantation; post-CRT: follow up after device implantation).
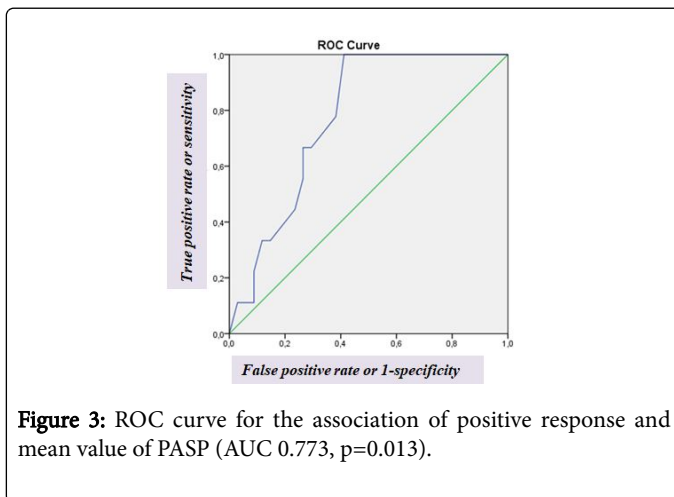
Two echocardiographic parameters selected by regression analysis were statistically significant for positive CRT response. It included lower PASP (odds ratio (OR) 1.152, 95.0%, confidence interval (CI) 1.026-1.293; p=0.017) and more severe MVR before treatment with CRT (OR 0.11, 95.0% CI 0.018-0.769; p=0.025). Pre-CRT PASP mean was a significant predictor for positive response with 91.2% of correct chance. The distribution of PASP means between groups is shown in Figure 2.
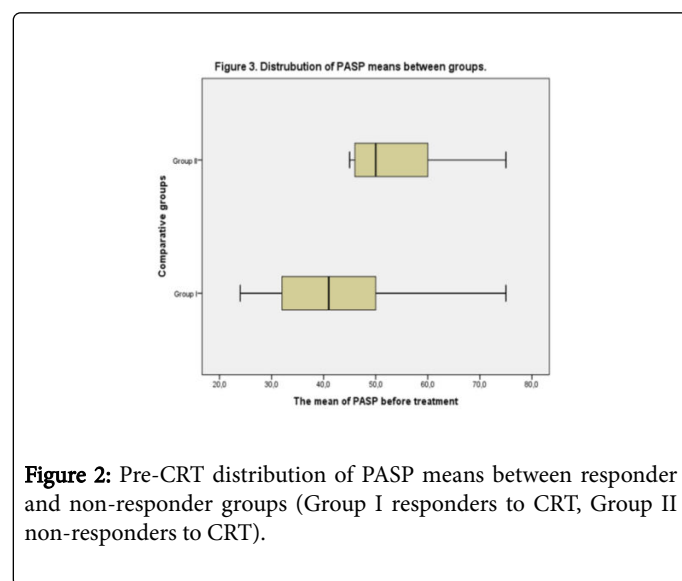
Figure 2: Pre-CRT distribution of PASP means between responder and non-responder groups (Group I responders to CRT, Group II non-responders to CRT).

Stepwise variable selection with forward selection and backward elimination demonstrated identical results. The precision of the model was verified with the Hosmer-Lemeshow test of goodness of fit test (p=0.715).

Statistically significant cut-off value of PASP was established in ROC analyses, with 78.0% of sensitivity and 62.0% of specificity. It demonstrated that PASP ≥ 46.0 mmHg is a predictor of poor response to CRT (Figure 3).

Figure 3: ROC curve for the association of positive response and mean value of PASP (AUC 0.773, p=0.013).

Discussion

The present study confirmed the reversible cardiac remodeling and improvement in systolic left ventricular function in heart failure patients treated with CRT. The significant increase in LVEF and reduction of left ventricular dilatation and grade of MVR revealed. The improvement in right ventricular function characteristics and decrease of pulmonary artery pressure were confirmed. The present findings are similar to previous studies, made by Rapacciuolo et al. and a MIRACLE trial [11-15].

Our study also confirmed that patients treated with CRT achieved significant improvement in their functional condition. We found significant decrease in NYHA functional class and improvement of distance walked in 6-minutes from 232.7 ± 69.7 m to 360.2 ± 83.3 m (p=0.000). The miracle trial results were quite similar to ours [15,16]. Other clinical trials MUSTIC, CONAK-CD, VENTAC-CHF/ CONTAK-CD results also demonstrated that 6 minute walk distance, quality of life, and NYHA class were significantly improved compared with control group, particularly in the NYHA class III-IV subgroup of patients [15,17].

Several studies have investigated the association between baseline QRS duration and QRS narrowing and reverse left ventricular remodeling during CRT. However, their results have been conflicting. Our current study revealed significant reduction in left ventricular electrical dyssynchrony and weak association between QRS duration and left ventricular volumes and systolic function. Interestingly, the ΔQRS was very similar in responders and non-responders groups, but electrical dyssynchrony after device implantation was significantly less in responders group (132.5 ± 14.3 ms *vs* 150.0 ± 8.9 ms, p=0.007). Coppola et al. in their study concluded that patients with a larger decrease in QRS duration after CRT initiation showed greater echocardiographic reverse remodeling [18]. Our findings confirm previous observations of Luparelli et al. that efficiency of CRT depended on the narrowing of QRS complex (127.0 ± 17.0 ms *vs* 141.0 ± 17.0 ms, p<0.05) [10].

Our current study shows a 77.1% prevalence of patients, responding to CRT. This finding is similar to previous studies, where nonresponders proportion ranged from 20% to 40% [8-11].

Analysis according to primary disease hasn't revealed ischemic cardiomyopathy as predictor of poor response to CRT as it was shown in previous studies [9]. However, established higher PASP in ischemic patient group and its predictive value capacitate to premise that ischemic patients are less likely to respond to CRT.

Predictors of response to CRT in chronic heart failure patients were analyzed by many clinical studies. CRT response criteria vary between clinical trials, so it is difficult to compare these trials with one another [9]. Possible markers predisposing positive response to CRT were also analyzed in our study. According to our study, lower pulmonary artery pressure and more severe mitral regurgitation prior to device implantation predicted favorable response to CRT. The criteria mentioned above are identified in other studies as well, so it's assumed, that efficiency of CRT can be attributed to multiple factors [9-12, 18-20].

Study Limitations and Future Arrangements

It is essential to acknowledge that possible limitation of our study is small number of subjects due to the small single-center study design.

Our study future goal is to expand the sample size, in order to assess CRT efficiency predictors more precisely.

Conclusions

Our study confirmed the reversible cardiac remodelling and improvement in systolic left and right ventricular function and functional condition in advanced heart failure patients treated with CRT. According to our study, lower pulmonary artery pressure and more severe mitral regurgitation prior to device implantation predicted favorable long-term response to CRT.

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