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ОРИГИНАЛЬНЫЕ ИССЛЕДОВАНИЯ

Clinical, electrical, and functional changes following CRT-P implantation: short-term results in patients with non-ischaemic cardiomyopathy

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Aim. Assessment of the correlation between cardiac remodeling, functional status and electrical remodeling after cardiac resynchronisation therapy (CRT) in patients with non-ischaemic cardiomyopathy.

Material and methods. A single center, prospective, observational study included 50 patients with non-ischaemic cardiomyopathy who were candidate for CRT implantation. All patients prior to CRT and then 3 months after implantation had standard 12-lead surface ECGs to assess QRSd for assessment electrical response, for assessment of left ventricular ejection fraction (LVEF) and volumes (left ventricular end diastolic and systolic volume, LVEDV and LVESV), mitral regurgitation (degree of mitral regurgitation), pulmonary artery systolic pressure (for diagnosis of pulmonary hypertension), NYHA class and 6 minute walk test (6MWT) to assess patient's functional capacity.

Results. 50 patients with CRT were included (35 males and 15 females, mean age 54.88±7.48 years). All patients were in sinus rhythm with QRS duration (QRSd) ⩾120 ms, EF<35% and left bundle branch block. After 3 months; there was significant improvement in QRSd in 82% of the cases (145.3±16.3 ms vs 133.3±17.2 ms, p<0.001). NYHA class improved at least one class in 78% and 6 min walk test improved in 80% (168.5 [131.0; 181.0] m vs 280.0 [237.0; 297.0] m, p<0.001). LVEF increased significantly in 74% of study cases (28.6±2.7 vs 34.5±3.1, p value 0.001) also there were statistically significant improvement in LVEDV (267.0±45.7 to 221.8±41.9 ml, p=0.002) and LVESV (137.43±47.19 to 105.03±42.7 ml, p=0.003). There was statistically significant correlation between QRSd and NYHA class (r=0.392, p=0.005), QRSd and 6MWT (r=0.323, p=0.022) and QRSd with LVEF (r=0.672 with p<0.001). Only seven patients showed improvement in the 3 parameters: LVESV, QRS duration and 6 min walk test.

Conclusion. The CRT-pacemaker implantation was associated with significant improvement in QRSd, NYHA class, 6MWT and LV volumes in the short-term period. QRSd improvement was significantly correlated with functional status and LV EF.

Keywords: CRT, cardiac remodeling, heart failure, NYHA class.

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Клинические, электрические и функциональные изменения после имплантации CRT-P: кратковременные результаты у пациентов с неишемической кардиомиопатией

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Цель. Оценить у пациентов с неишемической кардиомиопатией взаимосвязь между ремоделированием сердца, функциональным классом сердечной недостаточности и электрическим ремоделированием после сердечной ресинхронизирующей терапии (СРТ).

Материал и методы. В исследование включены 50 пациентов с неишемической кардиомиопатией, которым провели имплантацию СРТ. Всем пациентам исходно и через 3 мес после имплантации CRT проводилась стандартная ЭКГ в 12 отведениях для оценки QRSd (оценки электрического ответа), трансторакальная эхокардиография для оценки фракции выброса (ФВ) и объемов левого желудочка (конечный диастолический и систолический объем левого желудочка, КДО ЛЖ и КСО ЛЖ), митральной регургитации (степень митральной регургитации), систолического давления в легочной артерии (для диагностики легочной гипертензии), оценка функционального класса по NYHA и тест 6-минутной ходьбы (ТШХ) для оценки функциональных возможностей пациента.

Результаты. Средний возраст пациентов (35 мужчин и 15 женщин) составил 54,9±7,5 года. У всех пациентов – синусовый ритм (длительность QRS ⩾120 мс), ФВ <35% и блокада левой ножки пучка Гиса. Через 3 мес после имплантации СРТ в 82% случаев наблюдалось значимое изменение QRS (145,3±16,3 мс по сравнению с 133,3±17,2 мс, p<0,001). Класс NYHA улучшился по крайней мере на один у 78% пациентов, а показатели ТШХ – у 80% (168,5 [131,0; 181,0] м против 280,0 [237,0; 297,0] м, p<0,001). ФВ ЛЖ статистически значимо увеличилась у 74% пациентов (28,6±2,7 против 34,5±3,1, p<0,001), также значимо улучшились показатели: КДО ЛЖ (с 267,0±45,7 до 221,8±41,9 мл (p=0,002) и КСО ЛЖ (с 137,4±47,2 до 105,0±42,7 мл, p=0,003). Наблюдалась статистически значимая корреляция между продолжительностью интервала QRS и классом NYHA (r=0,392, p=0,005), QRS и результатом ТШХ (r=0,323, p=0,022) и длительностью QRS с ФВ ЛЖ (r=0,672 при p<0,001). Только у семи пациентов наблюдалось улучшение по всем трем параметрам: ФВ ЛЖ, длительность QRS и ТШХ.

Заключение. Проведение СРТ ассоциировалась со значительным улучшением показателей: длительность QRS, класс NYHA, дистанции в ТШХ и объем ЛЖ уже в краткосрочном периоде. Улучшение длительности интервала QRS значительно коррелировало с функциональным статусом и ФВ ЛЖ.

Ключевые слова: CRT, ремоделирование сердца, сердечная недостаточность, класс NYHA.

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Introduction

Intraventricular conduction delays are associated with dyssynchronous left ventricular (LV) contraction caused by regional delays in the electrical activation of the chamber. This phenomenon occurs in 15 to 30 percent of patients with heart failure due to dilated cardiomyopathy and reduced systolic function while increasing systolic volume [1].

In short-term studies, biventricular stimulation in the form of cardiac-resynchronisation therapy (CRT) has been shown to improve symptoms, enhance the quality of life, increase exercise tolerance, and partially reverse maladaptive remodeling [2].

When evaluating the responsiveness to CRT, it is preferable to consider decreased end-systolic volume to clinical parameters (such as New York Heart Association (NYHA) class, 6-minute walking test (6MWT), and quality of life score). Quality of life and reverse remodeling do not always align, as patients may experience improvement in one parameter without the other. Therefore, clinical parameters should not be disregarded, as an increase in quality of life or improvement in NYHA class can be just as significant as patient survival [3].

So, we aimed to study the short-term response to CRT regarding electrocardiography (ECG), cardiac remodeling and functional status to evaluate the overlap or the gap between these parameters which determine the response after device implantation.

Material and methods

A single center, prospective, observational study included 50 patients with non-ischaemic cardiomyopathy who were candidate for CRT implantation at National Heart Institute, Egypt in the period from October 2017 to June 2019. All patients had cardiac-resynchronisation therapy-pacemaker (CRT-P) devices (St. Jude) (the only available device at our institute). The study was approved by the local ethics committee and all patients signed informed consent.

Inclusion criteria:

- Patients with NYHA functional class III;
- Ambulatory patients with NYHA class IV who are heamodynamically stable for at least 4 weeks on optimal medical treatment;
- Left ventricular ejection fraction (LVEF) ⩽35%;
- Intraventricular conduction delay defined by a QRS duration (QRSd ⩾120 m sec if left bundle branch block or >140 msec if non left bundle branch block;
- All patients were on optimal recommended pharmacological heart failure therapy (angiotensin converting enzyme inhibitors or angiotensin receptor blockers, beta-blockers, aldosterone antagonists, and diuretic).

Exclusion criteria:

- Presence of atrial fibrillation;
- Amiodarone therapy;
- Complicated procedure or device failure;
- Severe comorbidities.

ECG acquisition and analysis

All patients had standard 12-lead ECGs (paper speed =25 mm/s, voltage gain =10 mm/mV) once prior to CRT implantation to assess QRSd then 3 months after implantation for assessment electrical response.

Echocardiography

All patients were examined using GE Vivid 7 machine M4S matrix sector array probe with a frequency range of 1.5 to 3.6 MHz (GE Vingmed Ultrasound, Horten, Norway) with integrated ECG recording [4] mostly with the patients lying in the left lateral decubitus position for assessment of:

- LV EF and volumes (left ventricular end diastolic and systolic volume, LVEDV and LVESV) were measured utilizing modified Simpson's equation (the endocardium of the apical two and four chamber echocardiographic views in systole and diastole is traced manually);
- Mitral regurgitation: degree of mitral regurgitation assessment according to the American Society of Echocardiography's consensus statement on echocardiographic quantification of valvular regurgitation and classified into mild, moderate and severe according to *vena contracta*;
- Pulmonary artery systolic pressure: for diagnosis of pulmonary hypertension. Pulmonary artery systolic pressure is estimated from the tricuspid regurgitant jet velocity using the modified Bernoulli equation and adding the estimated right atrial pressure on the basis of inferior vena cava diameter and collapsibility.

6 min walk test

This is a simple objective measurement to assess patient's functional capacity.

6MWT was performed indoors in a long, flat, straight, enclosed corridor with a hard surface. The walking course was 30 m in length. The length of the corridor is marked every 3 m. The turnaround point is marked with a cone. A starting line, which marks the beginning and end, is marked on the floor using brightly colored tape.

Reasons for immediately stopping a 6MWT include the following: chest pain, intolerable dyspnea, leg cramps, staggering, diaphoresis, and pale or ashen appearance. If a test is stopped for any of these reasons, the patient sits or lie supine as appropriate depending on the severity or the event and the technician's assessment of the severity of the event and the risk of syncope [5].

CRT implantation data

All patients had CRT-P devices (St. Jude medical, PM3140 DDDRV S/N 123456). Pacing leads were inserted through standard subclavian vein approach. Direct puncture of the subclavian vein was performed (Seldinger technique) with separate puncture for each lead (3 punctures in total). Dilators and peel-away sheaths were used to advance all pacing and defibrillation leads. Operators implanted right ventricle (RV) lead (pacing or implantable cardioverter-defibrillator) first, then the LV lead and finally the right atrium lead.

Device implantation

The generator was positioned over or under the pectoral muscle in CRT-P patients. The RA lead was placed in RA appendage, The RV lead tip was placed in the apex of the right ventricle. The LV lead tip was placed in the postero-lateral cardiac vein when possible or in an alternative posterior or lateral vein. The location chosen for LV lead was that giving the greatest spatial separation from the tip of the RV lead, with stable LV capture and without diaphragmatic capture at four times threshold voltage. Device programming using Merline St. Jude was done during follow up of the patients in the outpatient clinic to assess lead impedances, pacing, sensing thresholds, optimisation of AV and VV delays and detection of device malfunction [6].

We included only *de novo* implantation of devices and did not include generator changes, redo procedures, revisions.

Criteria of CRT response

All patients were evaluated after one month for device programming and after 3 months for evaluation of the response to CRT.

The response to CRT can be divided into 2 main categories:

1. Clinical endpoints indicating improved clinical status (NYHA functional class improvement by ⩾1 class, exercise capacity expressed as 6MWT)

2. Echocardiographic endpoints indicating improved LV systolic function or reversed LV remodeling (decrease in LVESV by ⩾15%) [6].

The improvement in 6MWT and NYHA class were considered as improved functional status.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation. Paired and unpaired and Student's t-test and nonparametric tests were used for comparisons between baseline and follow up. Categorical variable were expressed as numbers or percentages were analyzed with the chi-square test. D'Agostino-Pearson test for normal distribution was done and accordingly, non-parametric test was chosen when distribution was non-normal. Comparison between continuous data before and after CRT was done using paired t-test. Comparison between continuous data in responders and non-responders was done using unpaired t-test or Mann-Whitney test as appropriate. Correlations were made using Pearson correlation coefficient or Spearman r (S) as appropriate. P value was considered significant if <0.05.

Results

All patients were evaluated before CRT implantation and 3 months after for assessment of electrical remodeling, cardiac remodeling and functional status. All patients were in sinus rhythm, mean age was 54.88±7.48 years, 35 males (70%) and 15 female (30%), 24 patients (48%) were hypertensive, 22 patients (44%) had diabetes mellitus, 30 patients (60%) had dyslipidemia and 10 patients (20%) were smokers, all patients had DCM of non-ischaemic etiology.

ECG response to CRT

There was statistically significant improvement in QRS duration 3 months after CRT implantation in 41 patients (82%); where duration improved from 145.33±16.29 ms to 133.33±17.15 ms, P<0.001.

NYHA class improvement

Before CRT implantation; 72% of the patients were NYHA class III and 28% were NYHA class IV. After 3 months of CRT; 78% showed increase in NYHA by at least one class (fig. 1).

Six minutes walk test

The mean 6MWT distance at baseline was 168.5 meters reaching 280.0 meters 3 months after CRT implantation (p-value <0.001) (fig. 2). The improvement in the distance was detected in 40 cases (80%) that was considered as clinical response.

Cardiac remodeling and transthoracic echocardiographic response to CRT

There was statistically significant improvement in LVEF in 37 patients (74%), where EF% increased from 28.6±2.7 to 34.5±3.1 (p value <0.001). There was statistically significant improvement in LVEDV (267.0±45.7 to 221.8±41.9 ml, p=0.002), and LVESV (137.4±47.2 to 105.0±42.7 ml, p=0.003). The improvement occurred in 39 patients representing 78% of study cases.

Mitral regurgitation severity as assessed by *vena contracta* improved by one class (from moderate to mild) in 29 patients which represents 58% of study cases.

The correlation analysis between all parameters (ECG, echocardiographic and functional status)

Correlations between ECG parameter (QRSd) and changes in NYHA class, 6MWT and echocardiographic

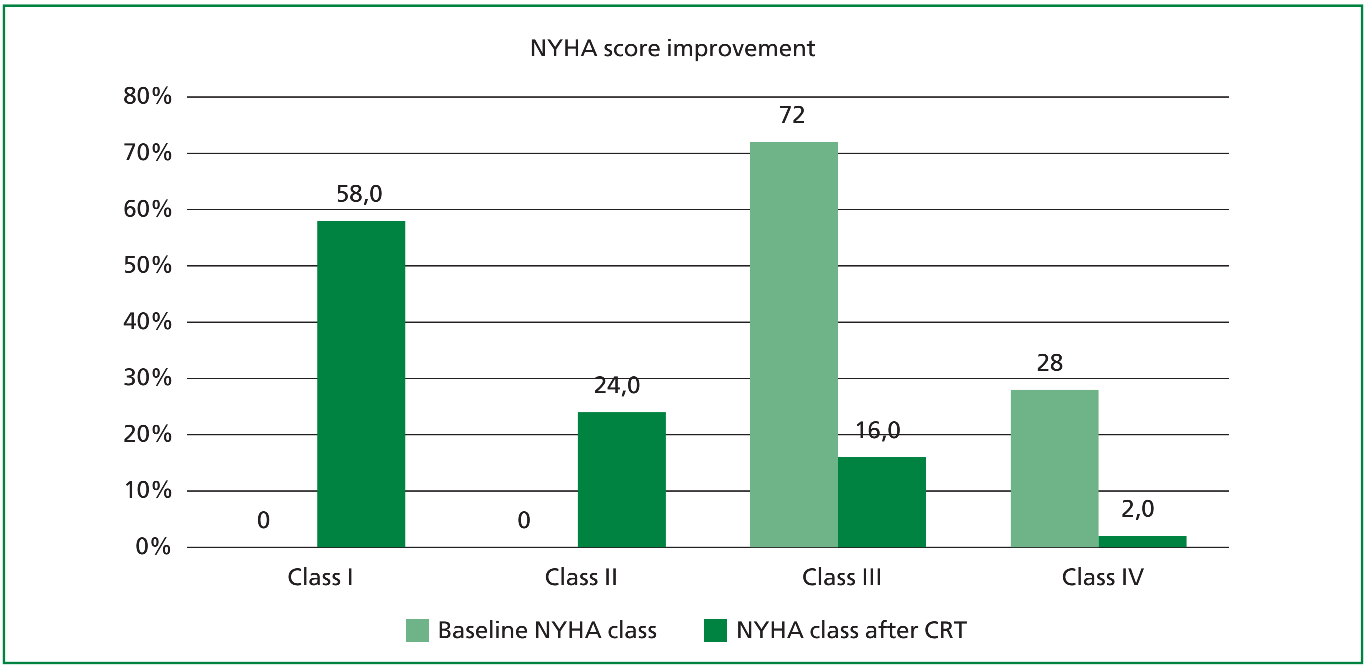

Figure 1. Bar chart showing NYHA class distribution among patients before and after CRT implantation

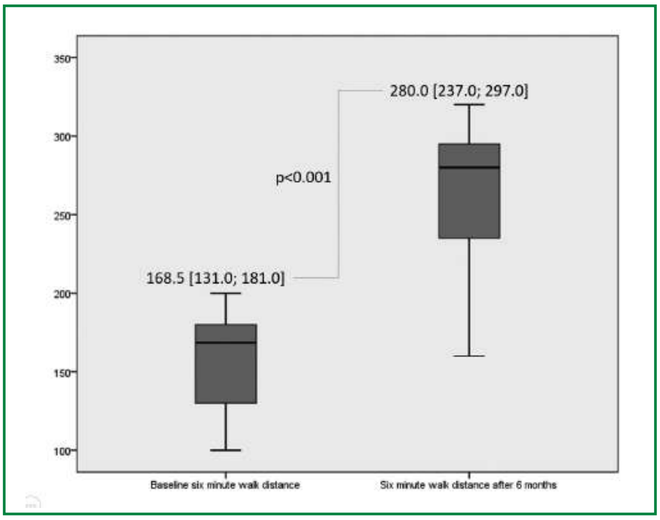

Figure 2. Box plot showing six-minute walk distance before and after CRT

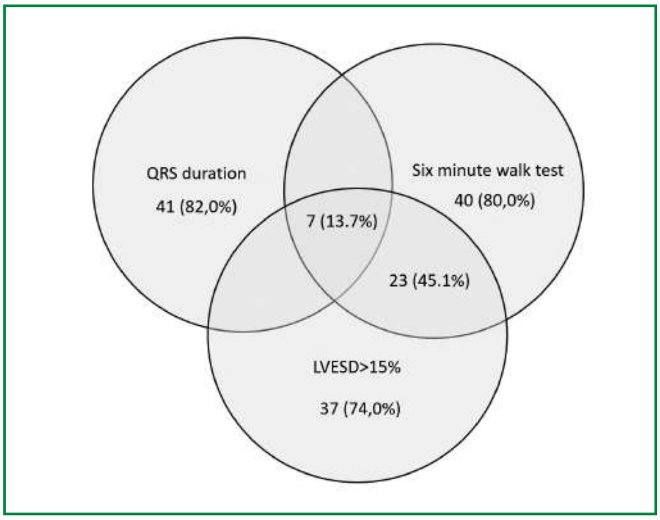

Figure 3. Diagram showing discrepancy in improvement of left ventricle end systolic volume (LV ESV), QRS duration and six-minute walk test

Table 1. Correlations between improvement in ECG parameters and changes in NYHA class, 6 min walk test and echocardiographic parameters

		NYHA improvement	EF improvement	LV EDV improvement	LV ESV improvement	Six-minute walk distance improvement
QRS improvement	r (S)	**0.392**	**0.672**	0.025	0.216	**0.323**
	P value	**0.005**	**0.0001**	0.864	0.131	**0.022**

LVESV – left ventricular end systolic volume, LVEDV – left ventricular end diastolic volume, LVEF – left ventricular ejection fraction, QRSD – QRS duration, r (S) – Spearman correlation coefficient

parameters revealed that; There was statistically significant correlation between changes in QRSd with NYHA class, QRSd with 6MWT and QRSd with LVEF, but it was insignificant for LVEDV and LVESV (table 1). Only seven patients showed improvement in the 3 parameters: LVESV, QRS duration and 6MWT (fig. 3).

Discussion

LV desynchrony was initially recognized as a phenomenon related to electrical conduction delay in patient with systolic heart failure with wide QRS complexes which is associated with worsening of symptoms and poor prognosis so; CRT is an important non-pharmacological therapy in end-stage heart failure if optimal heart failure therapy failed [7].

All patients in the present study had CRT-P according to the device availability and data available as it not clear whether adding implantable cardioverter-defibrillator as prophylactic therapy would be beneficial in patients who have advanced heart failure with severe left ventricular dysfunction or in those with non-ischaemic cardiomyopathies. Nor is it clear that in these settings, any benefit would be additive to those of CRT. According to COMPANION trial, the addition of a defibrillator to CRT did not appreciably affect the combined outcomes of death from or hospitalisation for any cause, which are heavily influenced by the hospitalisation components [8].

The researchers of COMPANION trial concluded that the decision of which of these two therapeutic options is appropriate for a particular setting is best determined on an individual basis by patients and their physicians [8].

Y. Liang et al., conducted a survey study where majority of CRT implantations were CRT-D, which occupied over 70-80% of all CRT devices in developed countries. However, this wide clinical application of CRT-D was not supported by solid evidence showing its superiority over CRT-P [9].

The present study included 50 patients referred for CRT implantation who were evaluated twice (before CRT and 3 months after) to evaluate cardiac remodeling, factional status and electrical remodeling after CRT implantation.

All CRT responders in this study had significant reduction in LVESV and LVEDV which is considered the hallmark of LV reverse remodeling, improved functional status (NYHA functional class, 6 min walk test) which was correlated with ECG changes (QRSd).

The results of our study are in agreement with C. Ypenburg et al. [10] who evaluated the clinical response to CRT where there was about 57% of the patients improved by one NYHA functional class and 12% showed an improvement of two NYHA functional classes while 31% remained unchanged for 6 months follow-up after CRT. The reason for unresponsiveness to CRT in this study was attributed to presence of a large percentage of ischaemic patients in the whole study which accounted for 68% compared to non-ischaemic patients.

C. Stellbrink et al. [11] studied 25 patients with advanced heart failure for 6 months follow up after CRT implantation with echocardiographic measurements of both dimensions and volumes, they found that the mean LVESV and LVEDV were significantly reduced after CRT. They concluded that spherical shape in dilated hearts was associated with increased wall stress, and that a change in LV sphericity have been correlated to an increase in exercise capacity and may involve a reduction in regional wall stress, myocardial oxygen demand and functional mitral regurgitation.

Mitral regurgitation is one of the echocardiographic changes that predict CRT reverses remodeling and clinical improvement. This improvement in mitral regurgitation could be explained by the effect of resynchronisation on the papillary muscles and the better coaptation of the leaflets. Also, the decrease in the contraction time possibly leads to a decrease in the degree of mitral regurgitation. The reverse remodeling and reduction of the LV dimensions can explain further improvement at follow-up [3].

In the present study clinical responders show corresponding increase in 6MWT coinciding with functional class improvement. The study of C. M. Yu [12] was in concordant to our study, where echocardiography show improvement in LVESV and LVEDV and improved 6MWT distance after pacing for 3 months that was associated with objective measurement of clinical improvement.

Our results agreed with the study of S. Cazeau et al. [13] who studied 100 patients with successful CRT implantation, they found that 63 patients had a decrease in QRS complex post CRT implantation and as the percentage of decrease in QRS width after implantation increased; there was an improvement in LVEF and clinical outcome post implantation.

Also, in a recent study by T. Nakai et al. [14] who studied 260 patients with a QRS duration >120 ms and a LVEF ⩽35% with follow up for 6 months, they found that after CRT implantation, the functional response definition of CRT response is associated with a higher response rate and better clinical outcomes than that of the echocardiographic response definition, and therefore it is reasonable to use the functional definition to assess CRT response.

A recent study examined the degree of agreement between echocardiographic and patient-reported health status response to CRT 6 months after implantation in 109 patients, and evaluated the differences in pre-implantation characteristics of patients with concordant and discordant echocardiographic and health status responses. They found that 25 (22.9%) had an echocardiographic response but no health status response and 29 (26.6%) had a health status response but no echocardiographic response [15]. Results of the PSYHEART-CRT study found that there is large discrepancy between echocardiographic and patient-reported health status response to CRT. The most important predictor of health status response was the pre-implantation health status score. These results emphasize that disease-specific health status measures may have additional value over 'objective' measures of CRT response and should be incorporated in clinical practice [15].

Clinical implication

The nonresponse rate for CRT is a significant concern. However, depending on the definition of response, there might not be as many non-responders as expected. In addition, functional responders can correctly predict better prognoses. So, we should evaluate the response to CRT regarding functional class improvement in association with ECG and echocardiography parameters.

Study limitation

Single center study that was conducted on small number of patients and the study was also limited by short term follow up.

Conclusion

The implantation of CRT-P was associated with significant improvement in QRSd, NYHA class, 6MWT and LV volumes already in the short-term period. QRSd improvement was significantly correlated functional status and left ventricle ejection.

Отношения и Деятельность. Нет.
Relationships and Activities. None.

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